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Occupational dust exposure contributes to overlapping chronic obstructive pulmonary disease and pneumoconiosis: a cross-sectional study

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ABSTRACT

Objectives Occupational dust exposure may induce various lung diseases, including pneumoconiosis and chronic obstructive pulmonary disease (COPD). The features of COPD and pneumoconiosis overlap have not been well described, and this may hamper management.This study aimed to describe the prevalence and characteristics as well as the risk factors of overlapping disease.

Design A cross-sectional study.

Setting and participants 758 patients with pneumoconiosis were recruited at a single-medical center.

Main outcome measures COPD was diagnosed according to a post bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio < 0.7. Clinical data were retrieved from predesigned medical reports. The patients underwent both chest radiograph and high-resolution computed tomography scan. Risk factors for COPD and pneumoconiosis overlapping were analyzed using regression analysis.

Results A cohort of 675 patients with pneumoconiosis, including asbestosis, silicosis, coal workers' pneumoconiosis and other pneumoconiosis, was eligible for analysis. COPD prevalence overall was 32.7% and was the highest in silicosis (40.0%) and coal workers' pneumoconiosis (38.6%). COPD prevalence increased with smoking pack-years, dust exposure duration and pneumoconiosis stage.Patients with overlapping disease had lower body mass index, higher smoking index and worse pulmonary function. Furthermore, 73.8% of pneumoconiosis had mild-to-moderate airflow limitation; 52.4% had airway hyperresponsiveness, and 43.9% had blood eosinophil count ≥100 cells/μL. Risk factors for overlapping disease included heavy smoking, silica or coal exposure and advanced pneumoconiosis. The interaction between dust exposure and smoking in COPD was also identified. The risk of COPD overlapping significantly increased with heavy smoking and silica or coal exposure [odds ratio 5.49, 95% confidence interval 3.04–9.93, p<0.001).

Conclusions COPD is highly prevalent in patients with pneumoconiosis, especially patients with silicosis and coal workers' pneumoconiosis. Occupational dust exposure is associated with an increased risk of COPD and pneumoconiosis overlapping, which

demands an effective preventive intervention.

Keywords: COPD, pneumoconiosis, dust exposure, prevalence, risk factor

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STRENGTHS AND LIMITATIONS OF THIS STUDY

The present study discloses the high prevalence of COPD with certain subtypes of pneumoconiosis in Chinese population.

The study consisted of a large sample size to identify the characteristics and risks for COPD and pneumoconiosis overlap.

The study was performed at a single centre and was limited by retrospective design.

Longitudinal and population-based study is warranted to identify the role of occupational dust exposure in the development combined COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), characterized by chronic airflow obstruction and persistent respiratory symptoms usually associated with inflammatory response to noxious particles and gasses,[1] is a serious public health problem worldwide.[2-4] In China, the most recent national survey of COPD with 50,991patients enrolled showed the prevalence of spirometry-defined COPD to be 8.6% (11.9% in men and 5.4% in women), representing an estimated 99.9 million population with COPD.[5] Similarly, the 2015 Global Burden of Disease study of 384 million adults found that 174.5 million adults were affected by COPD.[6] Cigarette smoking has been identified as the largest risk factor for COPD.[5 7 8] However, numerous other risk factors have been identified, including several rare genetic syndromes (such as α1-antitrypsin deficiency), underweight, occupational exposures and environmental pollution.[5 9] Additionally, the median population attributable fraction for occupational exposure contribution to COPD risk was 15% and was up to 31% among never-smokers.[7 10 11]

Specifically, occupational inorganic dust exposures (such as exposure to coal, silica, vanadium, osmium, cadmium, and welding fume dusts) introduce lung inflammation cascades and structural damage that can lead to various types of pneumoconiosis and to COPD.[12] Of note, pneumoconiosis is the most common occupational disease in China. In 2018, the prevalence was approximately 90% among the newly reported occupational patients, accounting for about 0.87 million Chinese people with pneumoconiosis.[13] Moreover, pneumoconiosis is a potential

cause of disability and thus induces a substantial socioeconomic burden, especially in developing countries. Interestingly, a study of 110,167 South African miners found that emphysema remains the occupational lung disease with the highest prevalence.[14] Previous research on COPD has mainly focused on the general population or workers with history of exposure to vapor gas, dust and fumes,[15] and few studies have investigated patients with COPD and pneumoconiosis overlap, which may be a distinct clinical phenotype. Furthermore, a substantial proportion of pneumoconiosis patients has a history of smoking, and it is unclear whether occupational dust exposure contribution to COPD is equipotent to that of cigarette smoking in some circumstances.

Therefore, the purpose of this study was 1) to describe the prevalence and clinical features of COPD and pneumoconiosis overlap and 2) to identify the risk factors for overlapping disease.

METHODS

Study design and population

This descriptive study adopted a cross-sectional design and followed guidelines established by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[16] Patients with pneumoconiosis were consecutively recruited, from January 2016 to July 2019, upon presentation at Beijing Chao-Yang Hospital, China, a regional medical center specializing in occupational medicine. The pneumoconiosis was diagnosed according to the International Labour

Organization classification after multidisciplinary discussion.[17] Patients of whom spirometry data were missing or with pulmonary malignant tumor, acute pulmonary infection, pulmonary tuberculosis, asthma, bronchiectasis, or pneumothorax were excluded. The most influential parameters of sample size were the risk factors for COPD and pneumoconiosis overlap. To identify the risk factors for overlapping disease, with 95% confidence and 80% power, 5-10 observations per previously demonstrated risk factors for COPD in pneumoconiosis patients were needed.[25] Based on the previous publication by Peng et al,[25] the prevalence of COPD among pneumoconiosis was 18.65%, the calculated sample size was 214-428.

All investigations were conducted in accordance with the ethical standards of Beijing Chao-Yang Hospital and the World Medical Association Declaration of Helsinki. The study was approved by the Institutional Review Board (IRB) of Beijing Chao-Yang Hospital. Written informed consent was obtained from all patients.

Study procedure

Clinical data were retrieved from medical reports and included age, sex, height, weight, smoking status, occupational history (including type of exposure, and start and end dates of employment), current and past medical history and family history. Smoking status was categorized as: current smoker, former smoker (cessation ≥12 months previously) and never-smoker. Smoking intensity was measured in pack-years (years of smoking 20 cigarettes/day), categorized as: 0 pack-years, 1–9 pack-years, 10–19 pack-years, and ≥20 pack-years, with “heavy smoking” defined as having

smoked ≥20 pack-years. Body mass index (BMI) was categorized as: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and overweight/obese (≥25.0 kg/m^2).[5] Latency, defined as the time from initial occupational dust exposure to pneumoconiosis diagnosis, was also recorded.

Pulmonary function tests were carried out by certified technicians according to hospital guidelines, which met the quality control standards established jointly by the American Thoracic Society and European Respiratory Society.[18] COPD was diagnosed based on clinical features and/or history of exposure to risk factors and post bronchodilator forced expiratory volume in 1 second (FEV_1)/ forced vital capacity (FVC) ratio <0.70, according to the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[19] Similarly, airflow limitation severity was categorized by the percentage of predicted FEV_1, as: mild (≥80%), moderate (≥50% to <80%), severe (≥30% to <50%) and very severe (<30%).[20] Airway hyperresponsiveness (AHR) was defined as an increase in FEV_1 of ≥200 mL and ≥12% after bronchodilation or positive methacholine bronchial challenge test.[21]

Chest radiographs were performed for each patient. These were independently assessed by two experienced clinicians according to the International Labor Organization classification,[17] with good interobserver correlation (0.81). Pneumoconiosis was classified as stage Ⅰ, II, or Ⅲ based on the density and distribution of small nodules / large opacities disclosed on the chest X-ray. Further details about the classificationcriteria can be found in theSupplementary Material (see

Method).

High-resolution computed tomography (HRCT) was acquired on a 64-slice single-source computed tomography (CT) system with 0.625–mm sections, a 1–sec scan time and a 10–mm interval in the apex–base scans, with the inclusion of both lungs in the field of view. Large opacity was defined as an opacity having the largest diameter (at the mediastinal window setting) >1 cm.The central type of large opacities, which compress the bronchus causing airway obstruction, is located between the transverse section of the tracheal carina and a margin 50 mm below the carina. A detailed description of the size of the large opacities is found in the Supplementary Material (see Method).

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 23 (IBM Inc, Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR). The comparisons of continuous variables were determined using the Mann–Whitney U test. Categorical variables were presented as number and percentage and were analyzed using the chi-square test. Univariate and multivariable logistic regression analyses were used to investigate previously demonstrated risk factors for COPD in all pneumoconiosis patients and in never-smokers, respectively, and were reported with odds ratio (OR) and confidence interval (CI). To eliminate the effect of mechanical compression on the bronchi, the patients with large opacities were excluded during Logistic regression analyses. A

p-value <0.05 was considered statistically significant.

Patient and public involvement statement

No patients or members of the public were involved in this study.

RESULTS

Demographics

A total 758 patients were invited to participate between January 2016 and July 2019. Of these, 675 patients with pneumoconiosis (523 men) were included in the analysis. The detailed flow diagram is shown in Figure 1. The sample included 130 patients with asbestosis, 210 with silicosis, 259 with coal workers' pneumoconiosis, and 76 with other subtypes of pneumoconiosis. The demographic characteristics of the groups are presented in Table 1.

Table 1 Demographics of the enrolled population

	All	Asbestosis	Silicosis	Coal workers' pneumoconiosis	Other pneumoconiosis	*p*-value
n	675	130	210	259	76	
Age, yrs	55.0 (49.0-65.0)	67.0 (63.0-72.0)	54.0 (48.0-63.0)	53.0 (49.0-58.0)	47.5 (42.0-55.0)	<0.001
Male	523 (77.5)	65 (50.0)	131 (62.4)	256 (98.8)	71 (93.4)	<0.001
BMI, kg/m^2	25.2±3.4	26.8±3.2	24.9±3.3	24.6±3.5	25.3±3.3	<0.001
Smoking exposure, pack-yrs						
0	290 (43.0)	80 (61.5)	119 (56.7)	71 (27.4)	20 (26.3)	<0.001
1-9	136 (20.1)	14 (10.8)	16 (7.6)	80 (30.9)	26 (34.2)	

10-19	94 (13.9)	10 (7.7)	23 (11.0)	48 (18.5)	13 (17.1)	
≥20	155 (23.0)	26 (20.0)	52 (24.8)	60 (23.2)	17 (22.4)	
Cumulative pack-yrs	15.0 (5.0-25.0)	21.3 (7.4-40.0)	20.0 (11.3-30.0)	10.5 (3.8-22.5)	10.0 (3.0-23.8)	<0.001
Duration of exposure, yrs	12.0 (7.0-20.0)	8.5 (5.0-14.3)	13.0 (8.0-21.3)	14.0 (6.0-20.0)	11.0 (8.0-17.5)	<0.001
Latent period, yrs	26.0 (13.0-35.0)	47.5 (36.5-52.0)	26.0 (18.0-34.0)	22.0 (9.0-29.0)	12.0 (8.0-22.8)	<0.001
Stage of pneumo.						<0.001
Ⅰ	332 (49.2)	85 (65.4)	95 (45.2)	89 (34.4)	63 (82.9)	
Ⅱ	164 (24.3)	39 (30.0)	44 (21.0)	72 (27.8)	9 (11.8)	
Ⅲ	179 (26.5)	6 (4.6)	71 (33.8)	98 (37.8)	4 (5.3)	

Datawas presented as mean ± SD or n (%) or median (IQR).

Abbreviations: BMI: body-mass index; IQR: interquartile range.

Prevalence of overlapping COPD and pneumoconiosis

The overall prevalence of spirometry-defined COPD was 32.7% (221/675) in the enrolled population (Table 2). The prevalence of COPD was significantly different among the subgroups, and patients with silicosis and coal workers' pneumoconiosis had relatively high prevalence (40.0% and 38.6% respectively). The prevalence of COPD increased with smoking pack-years and was 24.3%, 36.2% and 43.9%, respectively, in the patients smoking1–9 pack-years, 10–19 pack-years, and ≥20 pack-years (p<0.002). Similarly, the prevalence increased with the duration of dust exposure and was 30.0% with 0–15 years, 36.9% with 16–30 years and 39.6% with 31–45 years of exposure (p<0.046).The prevalence of COPD also increased with the pneumoconiosis stage and was 20.2% in stage Ⅰ, 25.6% in stage Ⅱ and 62.6% in

stage Ⅲ (p<0.001). The prevalence of COPD did not differ by sex, smoking history or BMI.

Table 2 Prevalence of COPD and pneumoconiosis overlap

	All		COPD and pneumoconiosis overlap		
	n	%	n	%	p-value
Overall	675	100	221	32.7	
Pneumoconiosis					<0.001
Asbestosis	130	19.3	23	17.7	
Silicosis	210	31.1	84	40.0	
Coal workers' pneumoconiosis	259	38.4	100	38.6	
Other pneumoconiosis	76	11.3	14	18.4	
Age, yrs					0.083
20-29	3	0.4	0	0	
30-39	25	3.7	4	16.0	
40-49	164	24.3	37	22.6	
50-59	222	32.9	95	42.8	
60-69	178	26.4	60	33.7	
≧70	83	12.3	25	30.1	
Male	523	77.5	177	33.8	0.258
Smoking history					0.089
Never-smoker	290	43.0	86	29.7	

Former smoker	183	27.1	68	37.2	
Current smoker	202	29.9	67	33.2	
Smoking exposure, pack-yrs					0.002
0	290	43.0	86	29.7	
1-9	136	20.1	33	24.3	
10-19	94	13.9	34	36.2	
≥20	155	23.0	68	43.9	
BMI, kg/m^2					0.228
<18.5	7	1.0	3	42.9	
18.5-24.9	330	48.9	115	34.8	
≥25.0	338	50.1	103	30.5	
Duration of exposure, yrs					0.046
0-15	424	62.8	127	30.0	
16-30	198	29.3	73	36.9	
31-45	53	7.9	21	39.6	
Stage of pneumoconiosis					<0.001
Ⅰ	332	49.2	67	20.2	
Ⅱ	164	24.3	42	25.6	
Ⅲ	179	26.5	112	62.6	

Abbreviations: COPD: chronic obstructive pulmonary disease; BMI: body-mass index.

Characteristics of the patient with overlapping COPD and pneumoconiosis

In comparison with pneumoconiosis alone, the patients with overlapping COPD and pneumoconiosis had higher cigarette pack-years(p<0.001), lower BMI(p=0.001),

higher silica or coal dust exposure(p<0.001) as well as higher stage(p<0.001) (Table 3). The patients with COPD and pneumoconiosis overlap also differed from those with only pneumoconiosis in a range of lung function measures (Table S1); in particular, compared with those without COPD, patients with COPD had significantly more severe airflow limitation, increased small airway dysfunction and decreased membrane diffusing capacity.

Among the 221 patients with COPD and pneumoconiosis, 31.7% had GOLD stage I COPD; 42.1% had stage II; 20.8% had stage III, and 5.4% had stage IV (Table S2); additionally, 52.4% (116/221) had a positive bronchodilation test or bronchial challenge test, and 43.9% (97/221) had blood eosinophil counts >100 cells/μL.

Risk factors for overlapping COPD and pneumoconiosis

In the full study sample, 9.5% (20/210) of the patients with silicosis and 1.5% (4/259) of the patients with coal workers' pneumoconiosis showed central of large opacities on HRCT, who were excluded during the logistic regression analyses. In the univariate logistic regression analysis, the risk factors associated with COPD included

Table 3 A composition of pneumoconiosis combined with or without COPD

	COPD and pneumoconiosis overlap	Pneumoconiosis alone	p-value
n	221	454	

Age, yrs	56.0 (51.0-63.5)	55.0 (48.0-65.3)	0.086
Male	177 (80.1)	346 (76.2)	0.258
Smoking exposure, pack-yrs			
0	86 (38.9)	204 (44.9)	0.002
1-9	33 (14.9)	103 (22.7)	
10-19	34 (15.4)	60 (13.2)	
≥20	68 (30.8)	87 (19.2)	
Cumulative pack-yrs	20.0 (10.0-30.0)	10.9 (4.0-22.5)	<0.001
BMI, kg/m^2	24.7 (22.2-26.7)	25.1 (23.3-27.9)	0.001
Duration of exposure, yrs	13.0 (7.0-20.0)	11.0 (6.0-19.0)	0.068
Latency period, yrs	25.0 (14.0-33.0)	26.0 (12.0-39.0)	0.320
Stage of pneumoconiosis			<0.001
Ⅰ	67 (30.3)	265 (58.4)	
Ⅱ	42 (19.0)	122 (26.9)	
Ⅲ	112 (50.7)	67 (14.8)	
Exposure dust			<0.001
Asbestos	23 (10.4)	107 (23.6)	
Silica	84 (38.0)	126 (27.8)	
Coal	100 (45.2)	159 (35.0)	
Other dust	14 (6.3)	62 (13.7)	
Symptoms			
Cough	171 (77.4)	329 (72.5)	0.172
Sputum production	123 (55.7)	219 (48.2)	0.070
Dyspnea	129 (58.4)	264 (58.1)	0.956

Data was presented as n (%) or median(IQR).

Abbreviations: COPD: chronic obstructive pulmonary disease; BMI: body-mass index.

age ≥40 years, heavy smoking, silica or coal exposure and pneumoconiosis stage Ⅲ (Table 4). In the multivariable-adjusted analyses, the risk of COPD was increased among patients with exposure to silica (OR 2.38, 95%CI 1.26–4.52, p=0.008) and coal (OR 3.09, 95%CI 1.52–6.27, p=0.002) dust, compared with patients with exposure to asbestos; there was a significantly increased risk of COPD in pneumoconiosis stage Ⅲ compared with stages Ⅰ/Ⅱ (OR 4.74, 95% CI 3.12–7.22, p<0.001).

Among the never-smokers, multivariable-adjusted analyses showed that the risk of COPD was increased with silica exposure (OR 3.62, 95%CI 1.40–9.34, p=0.008), and coal (OR 3.41, 95%CI 1.01–11.53, p=0.048) compared with asbestos exposure, consistent with the results for the full sample (Table S3).

Interaction between occupational dust exposure and cigarette smoking

A significant interaction was found between occupational exposure and cigarette smoking (Table S4 and Figure 2). The risk of COPD increased with heavy smoking and silica or coal exposure (OR 5.49, 95%CI 3.04–9.93, p<0.001). Similarly, a significant interaction was noted between smoking intensity and pneumoconiosis stage.

Table 4 Logistic regression model for 651 patients with COPD and pneumoconiosis overlap

	Univariate analysis	Multivariate analysis

	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age, yrs						
20-39	1.00	(ref)		1.00	(ref)	
40-59	3.86	1.14-13.06	0.030	2.32	0.64-8.51	0.203
≥60	3.46	1.01-11.82	0.048	3.61	0.93-13.98	0.064
Male gender	1.22	0.81-1.83	0.340	0.79	0.42-1.47	0.447
Smoking exposure, pack-yrs						
0	1.00	(ref)		1.00	(ref)	
1-19	1.01	0.68-1.49	0.980	0.95	0.57-1.60	0.852
≥20	2.01	1.32-3.06	0.001	1.97	1.14-3.42	0.016
BMI, kg/m^2						
<18.5 (underweight)	1.05	0.19-5.85	0.952	0.56	0.08-3.76	0.546
18.5-24.9 (normal)	1.00	(ref)		1.00	(ref)	
≥25.0 (overweight and obese)	0.87	0.63-1.22	0.431	1.10	0.76-1.60	0.622
Exposure duration, yrs						
0-15	1.00	(ref)		1.00	(ref)	
16-30	1.25	0.86-1.82	0.233	0.79	0.52-1.21	0.279
31-45	1.48	0.81-2.71	0.207	1.31	0.64-2.69	0.467
Exposure type						
Asbestos	1.00	(ref)		1.00	(ref)	
Silica	2.48	1.44-4.25	0.001	2.38	1.26-4.52	0.008
Coal	2.86	1.70-4.79	<0.001	3.09	1.52-6.27	0.002
Other dust	1.05	0.50-2.19	0.895	1.84	0.78-4.34	0.163
Stage of pneumoconiosis						

Ⅰ/Ⅱ	1.00	(ref)		1.00	(ref)	
Ⅲ	5.05	3.44-7.41	<0.001	4.74	3.12-7.22	<0.001
AHR						
Negative	1.00	(ref)		1.00	(ref)	
Positive	1.35	0.85-2.12	0.200	1.38	0.83-2.30	0.221

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate; BMI: body-mass index; AHR: airwayhyperresponsiveness.

DISCUSSION

To the best of our knowledge, our data are the first to disclose the high prevalence of COPD with certain types of pneumoconiosis. The data also identified the characteristics and risks for COPD and pneumoconiosis overlap. COPD was detected in 221/675 (32.7%) patients with pneumoconiosis. The prevalence of COPD differed according to the type of pneumoconiosis and was the highest in silicosis, followed by coal workers' pneumoconiosis. Patients with both COPD and pneumoconiosis had higher cigarette pack-years, lower BMI, higher composition of silica or coal dust exposure as well as higher percent of stageⅢ, more severe airflow limitation and increased small airway dysfunction, compared with patients with pneumoconiosis alone. Heavy smoking, silica or coal dust exposure and advanced pneumoconiosis were identified as the preventable risk factors for COPD in patients with pneumoconiosis. A positive interaction was found between occupational dust exposure and cigarette smoking among patients with COPD and pneumoconiosis overlap.

Previous population-based studies have reported different prevalence of COPD in various countries and on populations with a variety of occupations.[5 22 23] Data from 418,378 adult respondents to the 2017 Behavioral Risk Factor Surveillance System survey showed that the overall age-adjusted prevalence of COPD was 6.2% in the United States.[24] Similarly, the most recent population-based study from China reported an overall COPD prevalence of 8.6%.[5] Our data showed a particularly high prevalence of COPD among patients with pneumoconiosis, especially in silicosis and coal workers' pneumoconiosis. Across-sectional study of patients with silicosis or coal workers' pneumoconiosis from South China reported a COPD prevalence of 18.65% (119/638), which is lower than our finding.[25] One reason may be that our study had a higher percentage of smokers. It is also possible that the differences in COPD prevalence are a result of other differences in study participants and working conditions. The present study also found that over half (57.0%) of the patients were smokers and that the prevalence of COPD did not differ between smokers and nonsmokers—these findings are in line with the data reported by Peng et al.[25] While these earlier studies are not directly comparable, the data indicate that COPD and pneumoconiosis overlap occurs often in patients with certain types of pneumoconiosis.

Silica, coal, asbestos and mixed dusts are common occupational respiratory toxins. We found the prevalence of emphysema to be higher in the patients with silica exposure (55%) than in those with asbestos exposure(29%) (p=0.04).[26] A study from South Africa also showed that the rate (per 1000 autopsies) of emphysema was higher

with coal exposure (404/1000) than with asbestos exposure (345/1000).[27] Similarly, in the present study, the prevalence of COPD was twice as high in patients with silicosis and patients with coal workers' pneumoconiosis than in those with asbestosis. Of note, our previous study found that even in the presence of both emphysema and pulmonary fibrosis, spirometry may still be in normal range or show mild abnormalities, such as the small airway dysfunction.[28] Thus, it is possible that COPD was underestimated in patients with asbestosis.[28] Additionally, we found that pneumoconiosis severity was associated with COPD prevalence. This finding is consistent with previous data showing that the prevalence of emphysema increases with pneumoconiosis stage—as high as 60.76% (144/237) in pneumoconiosis stage Ⅲ.[29] These results suggest that airflow obstruction is associated with the severity of pneumoconiosis.[30 31]

The high prevalence of COPD in our sample of patients with pneumoconiosis underscores the importance of identifying the risk factors for COPD and pneumoconiosis overlap. Cigarette smoking has been well recognized as one of the main risk factors for development of COPD.[5 32 33] In the present study, smoking pack-years was associated with increased risk of COPD. However, in previous research, no significant correlation was found between smoking and COPD in patients with pneumoconiosis.[25] A possible explanation of the inconsistency is the lack of stratification by smoking pack-years in the earlier work. Previous studies of COPD have examined occupational risk factors in addition to smoking. An earlier meta-analysis showed that occupational exposure to irritant dusts, gases and fumes

was an independent risk factor for COPD.[34] Several studies have found that compared with asbestos dust, silica and coal dust exposure is more strongly associated with emphysema.[26 35 36] Similarly, the present study provides confirmation that exposure to silica or coal dust results in a higher risk for COPD than asbestos exposure does, both in smokers and never-smokers. These findings support the hypothesis that patients with silica and coal dust exposure suffer from higher dust concentrations or more damaging components (compared with asbestos), resulting in elevated risk for COPD. Inhaled silica and coal dust are predominantly deposited in the bronchioles, where they are engulfed by alveolar macrophages,[37-39] whereas inhaled asbestos fibers accumulate in the peribronchiolar and adjacent alveolar spaces.[40] Thus, different types of dust inflict varying damage to the lungs, but chronic inflammation, remodeling of the small airways and destruction of lung parenchyma ultimately lead to COPD.[41 42] Moreover, the higher OR for COPD among never-smokers compared with the full sample suggests that silica and coal dust exposures contribute more substantially to the burden of COPD in nonsmokers. Additionally, a longitudinal cohort study of 3,202 patients with silicosis in Hong Kong demonstrated interactive effects of cigarette smoking and silicosis on COPD.[43] Our study also indicates that smoking potentiates the effect of silica and coal dust exposure on COPD, consistent with the findings from other previous studies.[44-46] Thus, smoking cessation, in addition to prevention of occupational exposure, is critical to reducing COPD-related morbidity.

Among the full sample of patients with pneumoconiosis in the present study, nearly three-quarters of the cases of COPD were mild to moderate in severity (by

GOLD staging). The decline in lung function appears to result primarily from obstructive rather than restrictive air trapping. One-half of patients with COPD and pneumoconiosis overlap had AHR, but this was not significantly different from the finding of AHR in patients with pneumoconiosis alone. An earlier study reported that 24%–60% of patients with COPD had AHR.[47-49] However, little is known about the clinical features of COPD and pneumoconiosis overlap. A post hoc analysis of three randomized trials that included 4,528 patients with COPD treated by inhaled corticosteroids (ICS) found a reduction in exacerbation at blood eosinophil levels >100 cells/μL (relative risk =0.75).[50] Elsewhere, it was suggested that a threshold of ≥300 cells/μL can identify patients with the greatest likelihood of beneficial response to ICS.[50 51] Based on these studies, the 43.9% (97/221) of the patients with overlapping disease with blood eosinophil counts ≥100 cells/μL (or the 7.5% with counts >300 cells/μL) in the present study are likely to benefit from ICS. Nevertheless, it is uncertain whether blood eosinophil count is a reliable biomarker for response to ICS treatment for the prevention of exacerbations of COPD and pneumoconiosis overlap. Clinical trials are warranted to evaluate the effectiveness of ICS therapy in this regard.

This study had several limitations. First, this study recruited patients from a single medical centre and did not investigate dust-exposed workers without pneumoconiosis. Second, the cross-sectional design did not disclose the association between occupational exposure and disease progression or mortality—longitudinal, population-based studies are warranted to identify the role of occupational dust

exposure in the development and prevention of COPD. Third, since the patients in the study were employed by different industries, it was difficult to estimate occupational exposure levels and therefore the exposure-response relationship in COPD prevalence. Finally, the effect of passive smoke was not taken into account in our study.The effects of smoking on COPD might be underestimated.

In conclusion, the present study showed that COPD is highly prevalent in the patients with certain types of pneumoconiosis. More than 70% of patients with COPD and pneumoconiosis overlap had mild-to-moderate airflow limitation. Nearly half of them had AHR or peripheral eosinophil count >100/μL. Heavy smoking, silica or coal dust exposure and advanced pneumoconiosis are all associated with increased COPD risk, although differences in the onset of COPD before or after the onset of pneumoconiosis cannot be distinguished. In addition, occupational dust exposure interacts with smoking to further increase the risk of COPD. Our study indicates the high risk of occupational dust exposure for COPD and pneumoconiosis overlap and calls for urgent preventive intervention.

Contributors Y Fan performed all data collection, analyzed and wrote the manuscript. W Xu and Y Wang were responsible for data analyzing. Y Wang and S Yu were responsible for recruiting the patients. Q Ye contributed as primary investigator and was responsible for designing the study, recruiting the patients and writing the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Institutional Review Board (IRB) of Beijing Chao-Yang Hospital (2018-KE-119).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon request.

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Figure legends

Figure 1. Flow chart of the enrolled population

Figure 2. Interactions between risk factors for COPD and pneumoconiosis overlap: (A) occupational dust exposure and cigarette smoking, (B) pneumoconiosis stage and cigarette smoking. Abbreviation: COPD, chronic obstructive pulmonary disease

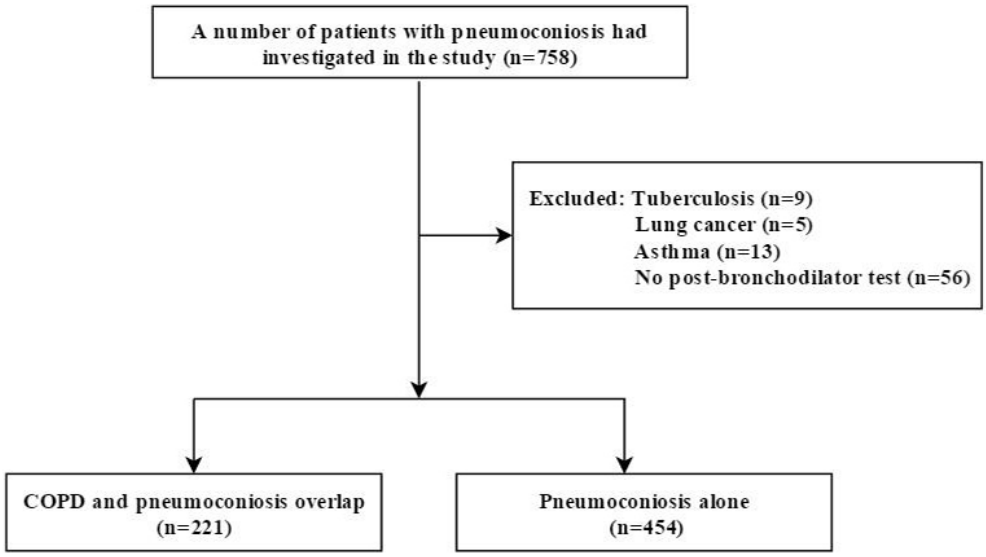

Figure 1. Flow chart of the enrolled population

65x37mm (300 x 300 DPI)

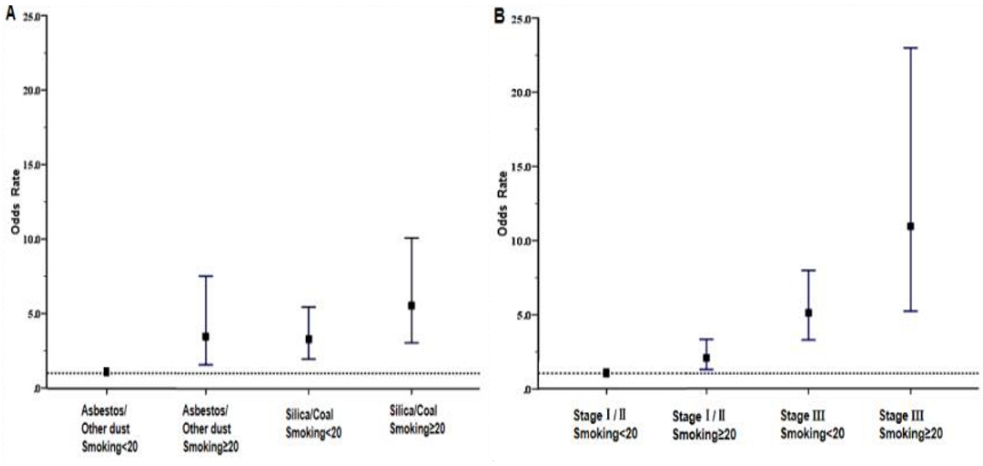

Figure 2. Interactions between risk factors for COPD and pneumoconiosis overlap: (A) occupational dust exposure and cigarette smoking, (B) pneumoconiosis stage and cigarette smoking. Abbreviation: COPD, chronic obstructive pulmonary disease

Supplimentary file

METHODS

Classification of pneumoconiosis by chest radiograph

Pneumoconiosis was classified into three stages according to the International Labour Organization classification system[1]. Briefly, each lung field was divided into three zones (upper, middle, lower) on the posterior chest radiographs. When the highest density of small opacities was ≥1/0, the distribution affected two or more zones and pleural plaques were apparent, the patients were diagnosed as Stage I. When the highest density of small opacities was ≥2/1 and the distribution affected more than four zones, or the highest density of small opacities was ≥3/2 and the distribution affected four or more zones, the patients were diagnosed as Stage II.When the highest density of small opacities was ≥3/2 and the distribution affected four or more zones with aggregation of small or large opacities, or the diameter of the largest opacity was ≥20 × 10 mm, the patients were diagnosed as Stage III. The interobserver correlation was good, and the κ value was 0.81.

High-resolution computed tomography

The size of large opacities were categorized as follows: (1) Type A: one or more opacities with total area ≤1/4 of the right side of the CT slice at the carina; (2) Type B: one or more opacities with total area >1/4 and ≤1/2 of the area of the right side of the CT slice at the carina; and (3) Type C: one or more opacities with total area >1/2

of the right side of the CT slice at the carina.[2] Two experts independently assessed the presence of large opacity on HRCT, according to the International Classification of HRCT for Occupational and Environmental Respiratory Diseases (ICOERD),[2] with good interobserver correlation (0.78).

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Table S1 Pulmonary function tests of the patients with COPD and pneumoconiosis overlap

Variables	All (n=675)	COPD and pneumoconiosis overlap (n=454)	Pneumoconiosis alone (n=221)	*p*-value
FVC, %pred	97.80 (82.30-109.40)	99.40 (85.50-110.15)	91.25 (76.00-109.18)	0.001
FEV_1, %pred	88.80 (71.40-102.20)	95.00 (82.80-105.95)	68.25 (49.45-86.33)	<0.001
FEV_1/FVC, %	74.18 (66.18-79.92)	77.97 (74.00-81.81)	61.21 (50.76-66.35)	<0.001
DLco SB, %pred	86.10 (68.20-99.60)	89.30 (74.25-100.65)	79.40 (60.25-92.95)	<0.001
TLC, %pred	93.50 (81.40-102.90)	90.50 (79.45-99.65)	99.30 (87.30-109.73)	<0.001
RV, %pred	102.20 (86.30-121.15)	95.00 (82.20-111.90)	120.95 (101.43-146.30)	<0.001
RV/TLC, %	40.53 (34.83-48.10)	37.81 (33.07-44.55)	46.47 (39.71-54.45)	<0.001
PEF, %pred	93.25 (74.23-109.00)	101.60 (89.00-115.10)	68.90 (46.43-86.05)	<0.001
MEF75, %pred	79.10 (52.75-105.00)	95.30 (77.25-112.60)	41.20 (22.95-56.55)	<0.001
MEF50, %pred	58.40 (38.40-79.50)	72.50 (56.05-89.45)	29.45 (18.10-41.48)	<0.001
MEF25, %pred	45.65 (29.70-61.90)	56.00 (42.40-69.95)	28.05 (19.75-37.35)	<0.001
PaO_2, mmHg	89.00 (83.00-96.00)	91.00 (85.00-97.00)	87.00 (81.00-93.00)	<0.001
CPI	13.80 (4.22-26.11)	12.90 (4.57-24.55)	15.78 (3.47-27.10)	0.314

Values were given as the median (IQR).

Abbreviations: FVC: forced vital capacity; FEV_1: forced expired volume in the first second; DLco SB: diffusion capacity for carbon monoxide of the lung single breath; TLC: total lung capacity; RV: residual volume; PEF: peak expiratory flow; MEF25: maximal expiratory flow after 25% of the FVC has been not exhaled. MEF50: maximal expiratory flow after 50% of the FVC has been not exhaled; MEF75: maximal expiratory flow after 75% of the FVC has been not exhaled; PaO_2: arterial partial pressure of oxygen; CPI: composite physiologic index; IQR: interquartile range.

Table S2 Characteristics of 221 patients with COPD and pneumoconiosis overlap

COPD and pneumoconiosis overlap	n	%
Classification of airflow limitation severity*		
GOLD stage I	70	31.7
GOLD stage II	93	42.1
GOLD stage Ⅲ	46	20.8
GOLD stage Ⅳ	12	5.4
AHR	116	52.4
Blood eosinophil count		
≥100 cells/μL	97	43.9
≥300 cells/μL	17	7.5

Abbreviations: COPD: chronic obstructive pulmonary disease; AHR:Airway hyperresponsiveness

* GOLD stage I: mild, FEV_1 ≥80% predicted; GOLD stage II: moderate, FEV_1 ≥50% to <80% predicted; GOLD stage III: severe, FEV_1 ≥30% to <50% predicted; GOLD stage IV: very severe, FEV_1<30% predicted

Table S3 Logistic regression model for 280 COPD and pneumoconiosis overlap in nonsmokers

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age, yrs						
20-39	1.00	(ref)		1.00	(ref)	
40-59	NS			NS		
≥60	NS			NS		
Male gender	0.92	0.54-1.57	0.770	0.93	0.42-2.04	0.860
BMI, kg/m^2						
<18.5 (underweight)	NS			NS		
18.5-24.9 (Normal)	1.00	(ref)		1.00	(ref)	
≥25.0 (Overweight and obese)	1.06	0.62-1.80	0.846	1.39	0.76-2.55	0.285
Exposure duration, yrs						
0-15	1.00	(ref)		1.00	(ref)	
16-30	1.22	0.65-2.27	0.533	0.89	0.44-1.84	0.760
31-45	0.69	0.19-2.54	0.576	0.71	0.17-3.01	0.645
Exposure type						
Asbestos	1.00	(ref)		1.00	(ref)	
Silica	2.76	1.35-5.63	**0.005**	3.62	1.40-9.34	**0.008**
Coal	2.47	1.14-5.36	**0.022**	3.41	1.01-11.53	**0.048**
Other dust	0.57	0.12-2.77	0.488	1.11	0.20-6.32	0.904
Stage of pneumoconiosis						
Ⅰ / Ⅱ	1.00	(ref)		1.00	(ref)	
Ⅲ	4.93	2.65-9.17	**<0.001**	4.50	2.28-8.90	**<0.001**

AHR						
Negative	1.00	(ref)		1.00	(ref)	
Positive	0.86	0.42-1.75	0.673	0.82	0.36-1.90	0.649

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate; BMI: body-mass index; AHR: airway hyperresponsiveness.

Table S4 Cumulative effects of cigarette smoking with occupational exposure on COPD in pneumoconiosis

		COPD and pneumoconiosis overlap	Pneumoconiosis alone	OR	95%CI	*p*-value
Exposure type	Smoking status					
Asbestos/Other dust	<20	22 (13.5)	141 (86.5)	1.00	(ref)	
Asbestos/Other dust	≥20	15 (34.9)	28 (65.1)	3.43	1.59-7.43	0.002
Silica/Coal	<20	115 (33.7)	226 (66.3)	3.26	1.97-5.39	<0.001
Silica/Coal	≥20	48 (46.2)	56 (53.8)	5.49	3.04-9.93	<0.001
Stage of pneumoconiosis	Smoking status					
Ⅰ/Ⅱ	<20	74 (19.1)	314 (80.9)	1.00	(ref)	
Ⅰ/Ⅱ	≥20	35 (32.4)	73 (67.6)	2.03	1.26-3.27	0.003
Ⅲ	<20	63 (54.3)	53 (45.7)	5.04	3.23-7.87	<0.001
Ⅲ	≥20	28 (71.8)	11 (28.2)	10.80	5.14-22.68	<0.001

Values were given as n (%)or OR (95%CI).

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Page 6

Study size	10	Explain how the study size was arrived at	Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6,7,11,12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	Page 8
		(*c*) Explain how missing data were addressed	Page 8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 8
		(*e*) Describe any sensitivity analyses	Page 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 9
		(b) Give reasons for non-participation at each stage	Page 5,6 and 8
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8 and 9
		(b) Indicate number of participants with missing data for each variable of interest	Patients of whom data were missing were excluded.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 9 and 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-14

		(*b*) Report category boundaries when continuous variables were categorized	Page 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 15-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Occupational dust exposure contributes to combined chronic obstructive pulmonary disease and pneumoconiosis: a cross-sectional study

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Occupational dust exposure contributes to combined chronic obstructive pulmonary disease and pneumoconiosis: a cross-sectional study

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Abstract

Objectives Occupational dust exposure may induce various lung diseases, including pneumoconiosis and chronic obstructive pulmonary disease (COPD). The features of combined COPD and pneumoconiosis have not been well described, and this may hamper the management. This study aimed to describe the prevalence and characteristics as well as the risk factors of the combined diseases.

Design A cross-sectional study.

Setting and participants 758 patients with pneumoconiosis were recruited at a single-medical center. Of these, 675 patients with pneumoconiosis, including asbestosis, silicosis, coal workers' pneumoconiosis and other pneumoconiosis, was eligible for analysis.

Primary outcome measures COPD was diagnosed based on clinical features and/or history of exposure to risk factors and post bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio < 0.7. Clinical data were collected from predesigned medical reports. The patients underwent both chest radiograph and high-resolution computed tomography scans. Risk factors for combined COPD and pneumoconiosis were analyzed using regression analysis.

Results COPD prevalence overall was 32.7% (221/675) and was the highest in silicosis (84/221) and coal workers' pneumoconiosis (100/221). COPD prevalence increased with smoking pack-years, dust exposure duration and pneumoconiosis stage. Patients with combined diseases had lower body mass index, higher smoking index and worse pulmonary function. Risk factors for combined diseases included heavy smoking, silica or coal exposure and advanced pneumoconiosis. The interaction between dust exposure and smoking in COPD was also identified. The risk of combined COPD significantly increased with heavy smoking and silica or coal exposure (odds ratio 5.49, 95% confidence interval 3.04–9.93, p<0.001).

Conclusions COPD is highly prevalent in patients with pneumoconiosis, especially patients with silicosis and coal workers' pneumoconiosis. Occupational dust exposure

as well as heavy smoking is associated with an increased risk of combined COPD and pneumoconiosis, which demands an effective preventive intervention.

Keywords: COPD, pneumoconiosis, dust exposure, prevalence, risk factor

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Strengths and limitations of this study

- A cross-sectional study was carried out to describe the prevalence and clinical features of combined chronic obstructive pulmonary disease (COPD) and pneumoconiosis.
- The risk factors for the combined diseases were analyzed using regression analysis in a cohort of patients with various subtypes of pneumoconiosis.
- The present study was limited by recruitment of the patients with pneumoconiosis of a single medical centre and the failure to enroll dust-exposed workers without pneumoconiosis.
- The cross-sectional design did not have the power to disclose the association between occupational exposure and disease progression or mortality.

Introduction

Pneumoconiosis is a group of heterogeneous fibrotic lung diseases that develops through the inhalation of the inorganic mineral dusts.[1] Till now, pneumoconiosis is the most common occupational disease in China. In 2018, the prevalence was approximately 90% among the newly reported occupational patients, accounting for about 0.87 million Chinese people with pneumoconiosis.[2] Moreover, pneumoconiosis is a potential cause of disability and thus induces a substantial socioeconomic burden, especially in developing countries.[3 4] A cohort of 110,167 South African miners was found that emphysema remains the occupational lung disease with the highest prevalence.[5] The occupational dust exposures induce lung inflammation cascades and structural damage that can lead dust-related lung disorders including pneumoconiosis as well as chronic obstructive pulmonary disease (COPD).[6]

COPD, characterized by chronic airflow obstruction and persistent respiratory symptoms usually associated with inflammatory response to noxious particles and gasses,[7] is a serious public health problem worldwide.[8-10] In China, the most recent national survey of COPD with 50,991patients enrolled showed the prevalence of spirometry-defined COPD to be 8.6% (11.9% in men and 5.4% in women), representing an estimated 99.9 million population with COPD.[11] Similarly, the 2015 Global Burden of Disease study of 384 million adults found that 174.5million adults were affected by COPD.[12] Cigarette smoking has been identified as the largest risk factor for COPD.[11 13 14] However, numerous other risk factors have been identified,

including several rare genetic syndromes (such as α1-antitrypsin deficiency), underweight, occupational exposures and environmental pollution.[11 15] Specifically, the median population attributable fraction for occupational exposure contribution to COPD risk was 15% and was up to 31% among never-smokers.[13 16 17] Previous research on COPD has mainly focused on the general population or workers with history of exposure to vapor gas, dust and fumes,[18] and few studies have investigated patients with combined COPD and pneumoconiosis, which may be a distinct clinical phenotype. Furthermore, a substantial proportion of pneumoconiosis patients have a history of smoking, and it is unclear whether occupational dust exposure contribution to COPD is equipotent to that of cigarette smoking in some circumstances.

Therefore, the purpose of this study was 1) to describe the prevalence and clinical features of combined COPD and pneumoconiosis and 2) to identify the risk factors for combined disease among pneumoconiosis patients.

Methods

Study design

This descriptive study adopted a cross-sectional design and followed guidelines established by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[19]

Settings and participants

Patients with pneumoconiosis were consecutively recruited, from January 2016 to July 2019, upon presentation at Beijing Chao-Yang Hospital, China, a regional medical center specializing in occupational medicine. The pneumoconiosis was diagnosed according to the International Labour Organization classification after multidisciplinary discussion.[20] Patients of whom spirometry data were missing or with pulmonary malignant tumor, acute pulmonary infection, pulmonary tuberculosis, asthma, bronchiectasis, or pneumothorax were excluded.

All investigations were conducted in accordance with the ethical standards of Beijing Chao-Yang Hospital and the World Medical Association Declaration of Helsinki. The study was approved by the Institutional Review Board (IRB) of Beijing Chao-Yang Hospital. Written informed consent was obtained from all patients.

Sample size

The most influential parameters of sample size were the risk factors for combined COPD and pneumoconiosis. To identify the risk factors for combined diseases, with 95% confidence and 80% power, 5-10 observations per previously demonstrated risk factors for COPD in pneumoconiosis patients were needed.[21] Based on the previous publication by Peng et al,[21] the prevalence of COPD among pneumoconiosis was 18.65%, the calculated sample size was 214 to 428. Furthermore, this study was demonstrated risk factors for COPD in never-smokers subgroup. Thus, the final sample sizes were 498 to 995 according to the proportion of non-smokers in patients with pneumoconiosis from Beijing Chao-Yang Hospital.

Study procedure

Data collection Clinical data were collected from medical reports and included age, sex, height, weight, smoking status, occupational history (including type of exposure, and start and end dates of employment), current and past medical history and family history at the date of inclusion. Smoking status was categorized as: current smoker, former smoker (cessation ≥12 months previously) and never-smoker. Smoking intensity was measured in pack-years (years of smoking 20 cigarettes/day), categorized as: 0 pack-years, 1–9 pack-years, 10–19 pack-years, and ≥20 pack-years, with "heavy smoking" defined as having smoked ≥20 pack-years. Body mass index (BMI) was categorized as: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and overweight/obese (≥25.0 kg/m^2).[11] Latency, defined as the time from initial occupational dust exposure to pneumoconiosis diagnosis, was also recorded.

Pulmonary function tests Pulmonary function tests were carried out by certified technicians according to hospital guidelines, which met the quality control standards established jointly by the American Thoracic Society and European Respiratory Society.[22] Pulmonary function parameters were measured using spirometry, whole body plethysmography, and single-breath diffusing capacity for carbon monoxide measurements. In this study, the pulmonary function prediction formula is based on the normal lung function prediction formula of Chinese adults established in 2017.[23] COPD was diagnosed based on clinical features and/or history of exposure to risk factors and post bronchodilator forced expiratory volume in 1 second (FEV_1)/ forced

vital capacity (FVC) ratio <0.70, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.[24] Similarly, airflow limitation severity was categorized by the percentage of predicted FEV_1, as: mild (≥80%), moderate (≥50% to <80%), severe (≥30% to <50%) and very severe (<30%).[25] Positive bronchial dilation test was defined as an increase in FEV_1 of ≥200 mL and ≥12% after bronchodilation (salbutamol 400mg).[24] Airway hyperresponsiveness (AHR) was defined by a methacholine provocation concentration of 4 mg/mL or less, which led to a 20% reduction in FEV_1 (PC_{20}).[26] Bronchial challenge test was performed in patients with FEV_1 above 60%.

Chest radiographs Chest radiographs were performed for each patient. These were independently assessed by two experienced clinicians according to the International Labor Organization classification,[20] with good interobserver correlation (0.81). Pneumoconiosis was classified as stage Ⅰ, II, or Ⅲ based on the density and distribution of small nodules / large opacities disclosed on the chest X-ray. Further details about the classification criteria can be found in the Supplementary Material (see Method).

High-resolution computed tomography (HRCT) HRCT was acquired on a 64-slice single-source CT system with 0.625–mm sections, a 1–sec scan time and a 10–mm interval in the apex–base scans, with the inclusion of both lungs in the field of view. Large opacity was defined as an opacity having the largest diameter (at the mediastinal window setting) >1 cm. The central type of large opacities, which

compress the bronchus causing airway obstruction, is located between the transverse section of the tracheal carina and a margin 50 mm below the carina. A detailed description of the size of the large opacities is found in the Supplementary Material (see Method).

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 23 (IBM Inc, Chicago, IL, USA). The distribution of the continuous variables was checked at first. Comparisons of normally distributed continuous variables were performed by a one-way analysis of variance (ANOVA) across four groups. The comparisons of non-normally distributed variables were determined using the Mann–Whitney U test or Kruskal-Wallis test. Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were presented as number and percentage and were analyzed using the chi-square test or Fisher's exact test. Univariate and multivariable logistic regression analyses were used to investigate previously demonstrated risk factors for COPD in all pneumoconiosis patients and in never-smokers, respectively, and were reported with odds ratio (OR) and confidence interval (CI). The possible interaction between occupational dust exposure and cigarette smoking was evaluated by Logistic regression analyses. To eliminate the effect of mechanical compression on the bronchi, the patients with large opacities were excluded during Logistic regression analyses. A p-value <0.05 was considered statistically significant.

Patient and public involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Results

Demographics

A total 758 patients were invited to participate between January 2016 and July 2019. Of these, 675 patients with pneumoconiosis (523 men) were included in the analysis. The detailed flow diagram is shown in Figure 1. The sample included 130 patients with asbestosis, 210 with silicosis, 259 with coal workers' pneumoconiosis, and 76 with other subtypes of pneumoconiosis. The demographic characteristics of the groups are presented in Table 1.

Table 1 Demographics of the enrolled population

	All	Asbestosis	Silicosis	Coal workers' pneumoconiosis	Other pneumoconiosis	*p*-value
n	675	130	210	259	76	
Age, yrs	55.0 (49.0-65.0)	67.0 (63.0-72.0)	54.0 (48.0-63.0)	53.0 (49.0-58.0)	47.5 (42.0-55.0)	<0.001
Male	523 (77.5)	65 (50.0)	131 (62.4)	256 (98.8)	71 (93.4)	<0.001
BMI, kg/m^2	25.2±3.4	26.8±3.2	24.9±3.3	24.6±3.5	25.3±3.3	<0.001
Smoking exposure,						
0	290 (43.0)	80 (61.5)	119 (56.7)	71 (27.4)	20 (26.3)	<0.001
1-9	136 (20.1)	14 (10.8)	16 (7.6)	80 (30.9)	26 (34.2)	
10-19	94 (13.9)	10 (7.7)	23 (11.0)	48 (18.5)	13 (17.1)	
≥20	155 (23.0)	26 (20.0)	52 (24.8)	60 (23.2)	17 (22.4)	

Cumulative pack-yrs	15.0 (5.0-25.0)	21.3 (7.4-40.0)	20.0 (11.3-30.0)	10.5 (3.8-22.5)	10.0 (3.0-23.8)	<0.001
Duration of exposure, yrs	12.0 (7.0-20.0)	8.5 (5.0-14.3)	13.0 (8.0-21.3)	14.0 (6.0-20.0)	11.0 (8.0-17.5)	<0.001
Latent period, yrs	26.0 (13.0-35.0)	47.5 (36.5-52.0)	26.0 (18.0-34.0)	22.0 (9.0-29.0)	12.0 (8.0-22.8)	<0.001
Stage of pneumo.						<0.001
Ⅰ	332 (49.2)	85 (65.4)	95 (45.2)	89 (34.4)	63 (82.9)	
Ⅱ	164 (24.3)	39 (30.0)	44 (21.0)	72 (27.8)	9 (11.8)	
Ⅲ	179 (26.5)	6 (4.6)	71 (33.8)	98 (37.8)	4 (5.3)	

Data was presented as mean ± SD or n (%) or median (IQR).

Abbreviations: BMI: body-mass index; IQR: interquartile range.

Prevalence of combined COPD and pneumoconiosis

The overall prevalence of COPD was 32.7% (221/675) in the enrolled population (Table 2). The prevalence of COPD was significantly different among the subgroups, and patients with silicosis and coal workers' pneumoconiosis had relatively high prevalence (40.0% and 38.6% respectively). The prevalence of COPD increased with smoking pack-years and was 24.3%, 36.2% and 43.9%, respectively, in the patients smoking1–9 pack-years, 10–19 pack-years, and ≥20 pack-years (p<0.002). Similarly, the prevalence increased with the duration of dust exposure and was 30.0% with 0–15 years, 36.9% with 16–30 years and 39.6% with 31–45 years of exposure (p<0.046). The prevalence of COPD also increased with the pneumoconiosis stage and was 20.2% in stage Ⅰ, 25.6% in stage Ⅱ and 62.6% in stage Ⅲ (p<0.001). The prevalence of COPD did not differ by sex, smoking history or BMI.

Table 2 Prevalence of combined COPD and pneumoconiosis

	All		COPD and pneumoconiosis		
	n	%	n	%	p-value

Overall	675	100	221	32.7	
Pneumoconiosis					<0.001
Asbestosis	130	19.3	23	17.7	
Silicosis	210	31.1	84	40.0	
Coal workers' pneumoconiosis	259	38.4	100	38.6	
Other pneumoconiosis	76	11.3	14	18.4	
Age, yrs					0.083
20-29	3	0.4	0	0	
30-39	25	3.7	4	16.0	
40-49	164	24.3	37	22.6	
50-59	222	32.9	95	42.8	
60-69	178	26.4	60	33.7	
≥70	83	12.3	25	30.1	
Male	523	77.5	177	33.8	0.258
Smoking history					0.089
Never-smoker	290	43.0	86	29.7	
Former smoker	183	27.1	68	37.2	
Current smoker	202	29.9	67	33.2	
Smoking exposure, pack-yrs					0.002
0	290	43.0	86	29.7	
1-9	136	20.1	33	24.3	
10-19	94	13.9	34	36.2	
≥20	155	23.0	68	43.9	
BMI, kg/m^2					0.228
<18.5	7	1.0	3	42.9	
18.5-24.9	330	48.9	115	34.8	
≥25.0	338	50.1	103	30.5	
Duration of exposure, yrs					0.046
0-15	424	62.8	127	30.0	
16-30	198	29.3	73	36.9	
31-45	53	7.9	21	39.6	
Stage of pneumoconiosis					<0.001
Ⅰ	332	49.2	67	20.2	
Ⅱ	164	24.3	42	25.6	
Ⅲ	179	26.5	112	62.6	

Abbreviations: COPD: chronic obstructive pulmonary disease; BMI: body-mass index.

Characteristics of the patient with combined COPD and pneumoconiosis

In comparison with pneumoconiosis alone, the patients with combined COPD and pneumoconiosis had higher cigarette pack-years (p<0.001), lower BMI (p=0.001), higher silica or coal dust exposure (p<0.001) as well as higher stage (p<0.001) (Table 3). The patients with combined COPD and pneumoconiosis also differed from those with only pneumoconiosis in a range of lung function measures (Table S1); in particular, compared with those without COPD, patients with COPD had significantly more severe airflow limitation, increased small airway dysfunction and decreased membrane diffusing capacity.

Among the 221 patients with COPD and pneumoconiosis, 31.7% had GOLD stage I COPD; 42.1% had stage II; 20.8% had stage III, and 5.4% had stage IV (Table S2). Additionally, 29.4% (65/221) patients with combined diseases had a positive bronchodilation test, 57.1% (64/112) had AHR, and 43.9% (97/221) had blood eosinophil counts >100 cells/μL (Table S2).

Risk factors for combined COPD and pneumoconiosis

In the full study sample, 9.5% (20/210) of the patients with silicosis and 1.5% (4/259) of the patients with coal workers' pneumoconiosis showed central of large opacities on HRCT, who were excluded during the logistic regression analyses. In the univariate logistic regression analysis, the risk factors associated with COPD included

Table 3 A composition of pneumoconiosis combined with or without COPD

	COPD and pneumoconiosis	Pneumoconiosis alone	*p*-value
n	221	454	
Age, yrs	56.0 (51.0-63.5)	55.0 (48.0-65.3)	0.086
Male	177 (80.1)	346 (76.2)	0.258
Smoking exposure, pack-yrs			
0	86 (38.9)	204 (44.9)	0.002
1-9	33 (14.9)	103 (22.7)	
10-19	34 (15.4)	60 (13.2)	
≥20	68 (30.8)	87 (19.2)	
Cumulative pack-yrs	20.0 (10.0-30.0)	10.9 (4.0-22.5)	<0.001
BMI, kg/m^2	24.7 (22.2-26.7)	25.1 (23.3-27.9)	0.001
Duration of exposure, yrs	13.0 (7.0-20.0)	11.0 (6.0-19.0)	0.068
Latency period, yrs	25.0 (14.0-33.0)	26.0 (12.0-39.0)	0.320
Stage of pneumoconiosis			<0.001
Ⅰ	67 (30.3)	265 (58.3)	
Ⅱ	42 (19.0)	122 (26.9)	
Ⅲ	112 (50.7)	67 (14.8)	
Exposure dust			<0.001
Asbestos	23 (10.4)	107 (23.6)	
Silica	84 (38.0)	126 (27.8)	
Coal	100 (45.2)	159 (35.0)	
Other dust	14 (6.3)	62 (13.7)	
Symptoms			
Cough	171 (77.4)	329 (72.5)	0.172
Sputum production	123 (55.7)	219 (48.2)	0.070
Dyspnea	129 (58.4)	264 (58.1)	0.956

Data was presented as n (%) or median (IQR).

Abbreviations: COPD: chronic obstructive pulmonary disease; BMI: body-mass index.

age ≥40 years, heavy smoking, silica or coal exposure and pneumoconiosis stage Ⅲ (Table 4). In the multivariable-adjusted analyses, the risk of COPD was increased among patients with exposure to silica (OR 2.42, 95%CI 1.28-4.59, p=0.007) and coal (OR 3.19, 95%CI 1.57-6.49, p=0.001) dust, compared with patients with exposure to

asbestos; there was a significantly increased risk of COPD in pneumoconiosis stage Ⅲ compared with stages Ⅰ/Ⅱ (OR 4.85, 95% CI 3.18-7.42, p<0.001).

Among the never-smokers, multivariable-adjusted analyses showed that the risk of COPD was increased with silica exposure (OR 3.88, 95%CI 1.49-10.12, p=0.006), and coal (OR 3.85, 95%CI 1.12-13.18, p=0.032) compared with asbestos exposure, consistent with the results for the full sample (Table S3).

Interaction between occupational dust exposure and cigarette smoking

A significant interaction was found between occupational exposure and cigarette smoking (Table S4 and Figure 2). The risk of COPD increased with heavy smoking and silica or coal exposure (OR 5.49, 95%CI 3.04–9.93, p<0.001). Similarly, a significant interaction was noted between smoking intensity and pneumoconiosis stage.

Table 4 Logistic regression model for 651 patients with combined COPD and pneumoconiosis*

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Age, yrs						
20-39	1.00	(ref)		1.00	(ref)	
40-59	3.86	1.14-13.06	0.030	2.33	0.64-8.54	0.202
≥60	3.46	1.01-11.82	0.048	3.76	0.97-14.7	0.056
Male gender	1.22	0.81-1.83	0.340	0.81	0.43-1.50	0.498
Smoking exposure, pack-yrs						
0	1.00	(ref)		1.00	(ref)	
1-19	1.01	0.68-1.49	0.980	0.92	0.55-1.56	0.761
≥20	2.01	1.32-3.06	0.001	1.91	1.10-3.32	0.022

BMI[#], kg/m^2						
<18.5	1.05	0.19-5.85	0.952	0.54	0.79-3.67	0.527
18.5-24.9	1.00	(ref)		1.00	(ref)	
≥25.0	0.87	0.63-1.22	0.431	1.09	0.75-1.58	0.664
Exposure duration, yrs						
0-15	1.00	(ref)		1.00	(ref)	
16-30	1.25	0.86-1.82	0.233	0.78	0.51-1.19	0.246
31-45	1.48	0.81-2.71	0.207	1.28	0.62-2.64	0.503
Exposure type						
Asbestos	1.00	(ref)		1.00	(ref)	
Silica	2.48	1.44-4.25	0.001	2.42	1.28-4.59	0.007
Coal	2.86	1.70-4.79	<0.001	3.19	1.57-6.49	0.001
Other dust	1.05	0.50-2.19	0.895	1.89	0.80-4.46	0.147
Stage of pneumoconiosis						
Ⅰ / Ⅱ	1.00	(ref)		1.00	(ref)	
Ⅲ	5.05	3.44-7.41	<0.001	4.85	3.18-7.42	<0.001
BDT						
Negative	1.00	(ref)		1.00	(ref)	
Positive	2.07	0.76-5.61	0.153	2.17	0.67-7.01	0.197

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate; BMI: body-mass index; BDT: bronchial dilation test.

*All variables in the table were included in the multivariate model, while adjusting for age, sex, BMI, exposure duration, and BDT.

[#] The patients with BMI <18.5 kg/m^2 means under weight, 18.5-24.9 kg/m^2 means normal range, and ≥25.0 kg/m^2 means overweight and obese.

Discussion

The present study disclosed that COPD was highly prevalent in the patients with certain types of pneumoconiosis. The results also showed the characteristics and risks for combined COPD and pneumoconiosis. The prevalence of COPD differed according to the type of pneumoconiosis and was the highest in silicosis, followed by coal workers' pneumoconiosis. Patients with both COPD and pneumoconiosis had higher cigarette pack-years, lower BMI, higher composition of silica or coal dust exposure as well as higher percent of stage Ⅲ, more severe airflow limitation and

increased small airway dysfunction, compared with patients with pneumoconiosis alone. Heavy smoking, silica or coal dust exposure and advanced pneumoconiosis were identified as the preventable risk factors for COPD in patients with pneumoconiosis. A positive interaction was found between occupational dust exposure and cigarette smoking among patients with combined COPD and pneumoconiosis.

Previous population-based studies have reported different prevalence of COPD in various countries and on populations with a variety of occupations.[11 27 28] Data from 418,378 adult respondents to the 2017 Behavioral Risk Factor Surveillance System survey showed that the overall age-adjusted prevalence of COPD was 6.2% in the United States.[29] Similarly, the most recent population-based study from China reported an overall COPD prevalence of 8.6%.[11] Our data showed a particularly high prevalence of COPD among patients with pneumoconiosis, especially in silicosis and coal workers' pneumoconiosis. Across-sectional study of patients with silicosis or coal workers' pneumoconiosis from South China reported a COPD prevalence of 18.65% (119/638), which is lower than our finding.[21] One reason may be that our study had a higher percentage of smokers. It is also possible that the differences in COPD prevalence are a result of other differences in study participants and working conditions. The present study also found that over half (57.0%) of the patients were smokers and that the prevalence of COPD did not differ between smokers and nonsmokers—these findings are in line with the data previously reported.[21] While these earlier studies are not directly comparable, the data indicate that combined

COPD and pneumoconiosis occurs often in patients with certain types of pneumoconiosis.

Silica, coal, asbestos and mixed dusts are common occupational respiratory toxins. One study found the prevalence of emphysema to be higher in the patients with silica exposure (55%) than in those with asbestos exposure (29%) (p=0.04).[30] Another study from South Africa also showed that the rate (per 1000 autopsies) of emphysema was higher with coal exposure (404/1000) than with asbestos exposure (345/1000).[31] Similarly, in the present study, the prevalence of COPD was twice as high in patients with silicosis and patients with coal workers' pneumoconiosis than in those with asbestosis. Of note, our previous study found that even in the presence of both emphysema and pulmonary fibrosis, spirometry may still be in normal range or show mild abnormalities, such as the small airway dysfunction.[32] Thus, it is possible that COPD was underestimated in patients with asbestosis.[32] Additionally, we found that pneumoconiosis severity was associated with COPD prevalence. This finding is consistent with previous data showing that the prevalence of emphysema increases with pneumoconiosis stage—as high as 60.76% (144/237) in pneumoconiosis stage Ⅲ.[33] These results suggest that airflow obstruction is associated with the severity of pneumoconiosis.[34 35]

The high prevalence of COPD in our sample of patients with pneumoconiosis underscores the importance of identifying the risk factors for combined COPD and pneumoconiosis. Cigarette smoking has been well recognized as one of the main risk

factors for development of COPD.[11 36 37] In the present study, smoking pack-years was associated with increased risk of COPD. However, in previous research, no significant correlation was found between smoking and COPD in patients with pneumoconiosis.[21] A possible explanation of the inconsistency is the lack of stratification by smoking pack-years in the earlier work. Previous studies of COPD have examined occupational risk factors in addition to smoking. An earlier meta-analysis showed that occupational exposure to irritant dusts, gases and fumes was an independent risk factor for COPD.[38] Several studies have found that compared with asbestos dust, silica and coal dust exposure is more strongly associated with emphysema.[30 39 40] Similarly, the present study provides confirmation that exposure to silica or coal dust results in a higher risk for COPD than asbestos exposure does, both in smokers and never-smokers. These findings support the hypothesis that patients with silica and coal dust exposure suffer from higher dust concentrations or more damaging components (compared with asbestos), resulting in elevated risk for COPD. Inhaled silica and coal dust are predominantly deposited in the bronchioles, where they are engulfed by alveolar macrophages,[41-43] whereas inhaled asbestos fibers accumulate in the peribronchiolar and adjacent alveolar spaces.[44] Thus, different types of dust inflict varying damage to the lungs, but chronic inflammation, remodeling of the small airways and destruction of lung parenchyma ultimately lead to COPD.[45 46] Moreover, the higher OR for COPD among never-smokers compared with the full sample suggests that silica and coal dust exposures contribute more substantially to the burden of COPD in nonsmokers. Additionally, a longitudinal cohort study of

3,202 patients with silicosis in Hong Kong demonstrated interactive effects of cigarette smoking and silicosis on COPD.[47] Our study also indicates that smoking potentiates the effect of silica and coal dust exposure on COPD, consistent with the findings from other previous studies.[48-50] Thus, smoking cessation, in addition to prevention of occupational exposure, is critical to reducing COPD-related morbidity.

Among the full sample of patients with pneumoconiosis in the present study, nearly three-quarters of the cases of COPD were mild to moderate in severity (by GOLD staging). The decline in lung function appears to result primarily from obstructive rather than restrictive air trapping. One-half of patients with combined COPD and pneumoconiosis had AHR, but this was not significantly different from the finding of AHR in patients with pneumoconiosis alone. An earlier study reported that 24%–60% of patients with COPD had AHR.[51-53] However, little is known about the clinical features of combined COPD and pneumoconiosis. A post hoc analysis of three randomized trials that included 4,528 patients with COPD treated by inhaled corticosteroids (ICS) found a reduction in exacerbation at blood eosinophil levels >100 cells/μL (relative risk =0.75).[54] Elsewhere, it was suggested that a threshold of ≥300 cells/μL can identify patients with the greatest likelihood of beneficial response to ICS.[54 55] Based on these studies, the 43.9% (97/221) of the patients with combined disease with blood eosinophil counts ≥100 cells/μL (or the 7.5% with counts >300 cells/μL) in the present study are likely to benefit from ICS. Nevertheless, it is uncertain whether blood eosinophil count is a reliable biomarker for response to ICS treatment for the prevention of exacerbations of combined COPD and

pneumoconiosis. Clinical trials are warranted to evaluate the effectiveness of ICS therapy in this regard.

This study had several limitations. First, this study recruited patients from a single medical centre and did not investigate dust-exposed workers without pneumoconiosis. Second, the cross-sectional design did not disclose the association between occupational exposure and disease progression or mortality—longitudinal, population-based studies are warranted to identify the role of occupational dust exposure in the development and prevention of COPD. Third, since the patients in the study were employed by different industries, it was difficult to estimate occupational exposure levels and therefore the exposure-response relationship in COPD prevalence. Finally, the effect of passive smoke was not taken into account in our study. The effects of smoking on COPD might be underestimated.

Conclusion

The present study showed that COPD was highly prevalent in the patients with certain types of pneumoconiosis. More than 70% of patients with combined COPD and pneumoconiosis had mild-to-moderate airflow limitation. Nearly half of them had peripheral eosinophil count >100/μL. Heavy smoking, silica or coal dust exposure and advanced pneumoconiosis are all associated with increased COPD risk, although differences in the onset of COPD before or after the onset of pneumoconiosis cannot be distinguished. In addition, occupational dust exposure interacts with smoking to further increase the risk of COPD. Our study indicates that the prevention measures

are critical to decrease the occupational exposure and improve the disease controlling among dust exposure workers. Meanwhile, tobacco education and smoking cessation are needed to recognize and control smoking hazards.

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Footnotes

Contributors: Y Fan performed all data collection, analyzed and wrote the manuscript. W Xu and Y Wang were responsible for acquisition of data and data analysis. Y Wang and S Yu were responsible for recruiting the patients and acquisition of data. Q Ye contributed as primary investigator and was involved in the conception, design and planning the study, the acquisition of data, revision of the paper. All authors contributed to data interpretation, read and approved the final manuscript.

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Figure legends

Figure 1. Flow chart of the enrolled population

Figure 2. Interactions between risk factors for combined COPD and pneumoconiosis: (A) occupational dust exposure and cigarette smoking, (B) pneumoconiosis stage and cigarette smoking

Abbreviation: COPD: chronic obstructive pulmonary disease.

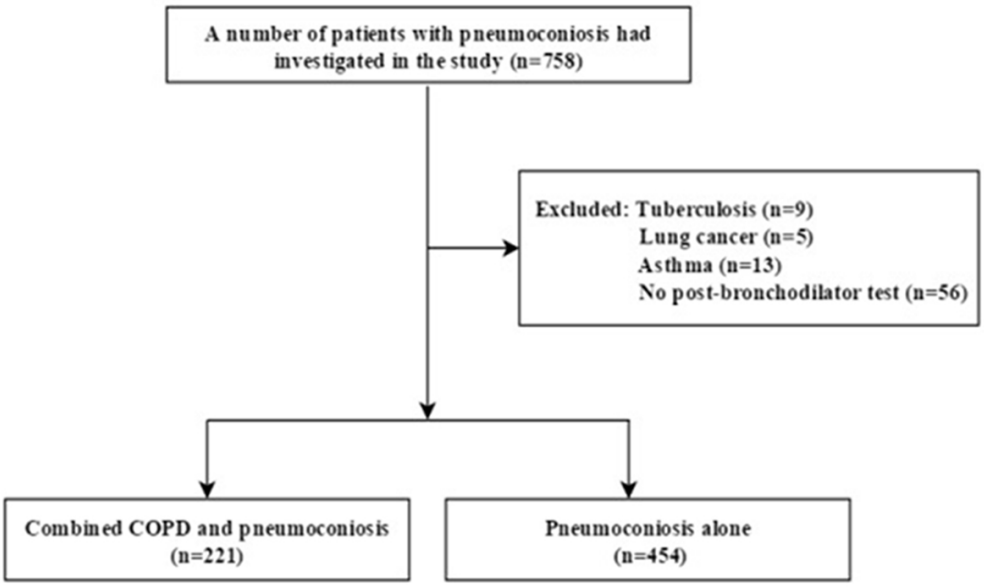

Figure 1. Flow chart of the enrolled population

99x60mm (300 x 300 DPI)

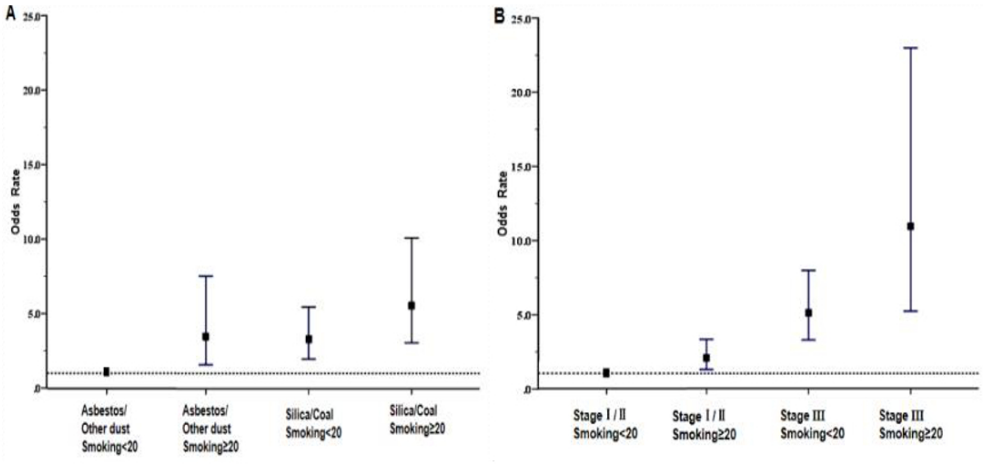

Figure 2. Interactions between risk factors for combined COPD and pneumoconiosis: (A) occupational dust exposure and cigarette smoking, (B) pneumoconiosis stage and cigarette smoking
Abbreviation: COPD: chronic obstructive pulmonary disease.

Supplimentary files

Methods

Classification of pneumoconiosis by chest radiograph

Pneumoconiosis was classified into three stages according to the International Labour Organization classification system.[1] Briefly, each lung field was divided into three zones (upper, middle, lower) on the posterior chest radiographs. When the highest density of small opacities was ≥1/0, the distribution affected two or more zones and pleural plaques were apparent, the patients were diagnosed as Stage I. When the highest density of small opacities was ≥2/1 and the distribution affected more than four zones, or the highest density of small opacities was ≥3/2 and the distribution affected four or more zones, the patients were diagnosed as Stage II. When the highest density of small opacities was ≥3/2 and the distribution affected four or more zones with aggregation of small or large opacities, or the diameter of the largest opacity was ≥20 × 10 mm, the patients were diagnosed as Stage III. The interobserver correlation was good, and the κ value was 0.81.

High-resolution computed tomography

The size of large opacities were categorized as follows: (1) Type A: one or more opacities with total area ≤1/4 of the right side of the CT slice at the carina; (2) Type B: one or more opacities with total area >1/4 and ≤1/2 of the area of the right side of the CT slice at the carina; and (3) Type C: one or more opacities with total area >1/2 of

the right side of the CT slice at the carina.[2] Two experts independently assessed the presence of large opacity on HRCT, according to the International Classification of HRCT for Occupational and Environmental Respiratory Diseases (ICOERD),[2] with good interobserver correlation (0.78).

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Table S1 Pulmonary function tests of the patients with combined COPD and pneumoconiosis

Variables	All (n=675)	COPD and pneumoconiosis (n=221)	Pneumoconiosis alone (n=454)	*p*-value
FVC, %pred	97.80 (82.30-109.40)	91.25 (76.00-109.18)	99.40 (85.50-110.15)	0.001
FEV_1, %pred	88.80 (71.40-102.20)	68.25 (49.45-86.33)	95.00 (82.80-105.95)	<0.001
FEV_1/FVC, %	74.18 (66.18-79.92)	61.21 (50.76-66.35)	77.97 (74.00-81.81)	<0.001
DLco SB, %pred	86.10 (68.20-99.60)	79.40 (60.25-92.95)	89.30 (74.25-100.65)	<0.001
TLC, %pred	93.50 (81.40-102.90)	99.30 (87.30-109.73)	90.50 (79.45-99.65)	<0.001
RV, %pred	102.20 (86.30-121.15)	120.95 (101.43-146.30)	95.00 (82.20-111.90)	<0.001
RV/TLC, %	40.53 (34.83-48.10)	46.47 (39.71-54.45)	37.81 (33.07-44.55)	<0.001
PEF, %pred	93.25 (74.23-109.00)	68.90 (46.43-86.05)	101.60 (89.00-115.10)	<0.001
MEF_{75}, %pred	79.10 (52.75-105.00)	41.20 (22.95-56.55)	95.30 (77.25-112.60)	<0.001
MEF_{50}, %pred	58.40 (38.40-79.50)	29.45 (18.10-41.48)	72.50 (56.05-89.45)	<0.001
MEF_{25}, %pred	45.65 (29.70-61.90)	28.05 (19.75-37.35)	56.00 (42.40-69.95)	<0.001
PaO_2, mmHg	89.00 (83.00-96.00)	87.00 (81.00-93.00)	91.00 (85.00-97.00)	<0.001
CPI	13.80 (4.22-26.11)	15.78 (3.47-27.10)	12.90 (4.57-24.55)	0.314

Values were given as the median (IQR).

Abbreviations: FVC: forced vital capacity; FEV_1: forced expired volume in the first second; DLco SB: diffusion capacity for carbon monoxide of the lung single breath; TLC: total lung capacity; RV: residual volume; PEF: peak expiratory flow; MEF_{25}: maximal expiratory flow after 25% of the FVC has been not exhaled. MEF_{50}: maximal expiratory flow after 50% of the FVC has been not exhaled; MEF_{75}: maximal expiratory flow after 75% of the FVC has been not exhaled; PaO_2: arterial partial pressure of oxygen; CPI: composite physiologic index; IQR: interquartile range.

Table S2 Characteristics of 221 patients with combined COPD and pneumoconiosis

COPD and pneumoconiosis	n	%
Classification of airflow limitation severity*		
GOLD stage I	70	31.7
GOLD stage II	93	42.1
GOLD stage III	46	20.8
GOLD stage IV	12	5.4
BDT, positive	65	29.4
AHR†	64	57.1
Blood eosinophil count		
≥100 cells/μL	97	43.9
≥300 cells/μL	17	7.5

Abbreviations: COPD: chronic obstructive pulmonary disease; BDT: bronchial dilation test; AHR: airway hyperresponsiveness.

* GOLD stage I: mild, FEV_1 ≥80% predicted; GOLD stage II: moderate, FEV_1 ≥50% to <80% predicted; GOLD stage III: severe, FEV_1 ≥30% to <50% predicted; GOLD stage IV: very severe, FEV_1<30% predicted.

†Bronchial challenge test was performed in patients with FEV_1 predicted more than 60%. In present cohort of combined COPD and pneumoconiosis, 57.1% (64/112) was shown AHR.

Table S3 Logistic regression model for 280 combined COPD and pneumoconiosis in nonsmokers

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age, yrs						
20-39	1.00	(ref)		1.00	(ref)	
40-59	NS			NS		
≥60	NS			NS		
Male gender	0.92	0.54-1.57	0.770	0.95	0.43-2.08	0.946
BMI, kg/m^2						
<18.5 (underweight)	NS			NS		
18.5-24.9 (Normal)	1.00	(ref)		1.00	(ref)	
≥25.0 (Overweight and	1.06	0.62-1.80	0.846	1.35	0.735-2.47	0.335
Exposure duration, yrs						
0-15	1.00	(ref)		1.00	(ref)	
16-30	1.22	0.65-2.27	0.533	0.85	0.41-1.75	0.651
31-45	0.69	0.19-2.54	0.576	0.67	0.16-2.87	0.590
Exposure type						
Asbestos	1.00	(ref)		1.00	(ref)	
Silica	2.76	1.35-5.63	**0.005**	3.88	1.49-10.12	**0.006**
Coal	2.47	1.14-5.36	**0.022**	3.85	1.12-13.18	**0.032**
Other dust	0.57	0.12-2.77	0.488	1.18	0.21-6.72	0.849
Stage of pneumoconiosis						
I/II	1.00	(ref)		1.00	(ref)	
III	4.93	2.65-9.17	**<0.001**	4.74	2.38-9.43	**<0.001**
BDT						
Negative	1.00	(ref)		1.00	(ref)	
Positive	1.57	0.85-2.87	0.147	1.50	0.75-3.03	0.256

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate; BMI: body-mass index; BDT: bronchial dilation test.

Table S4 Cumulative effects of cigarette smoking with occupational exposure on COPD in pneumoconiosis

		COPD and pneumoconiosis	Pneumoconiosis alone	OR	95%CI	*p*-value
Exposure type	Smoking status					
Asbestos/Other dust	<20	22 (13.5)	141 (86.5)	1.00	(ref)	
Asbestos/Other dust	≥20	15 (34.9)	28 (65.1)	3.43	1.59-7.43	0.002
Silica/Coal	<20	115 (33.7)	226 (66.3)	3.26	1.97-5.39	<0.001
Silica/Coal	≥20	48 (46.2)	56 (53.8)	5.49	3.04-9.93	<0.001
Stage of pneumoconiosis	Smoking status					
I/II	<20	74 (19.1)	314 (80.9)	1.00	(ref)	
I/II	≥20	35 (32.4)	73 (67.6)	2.03	1.26-3.27	0.003
III	<20	63 (54.3)	53 (45.7)	5.04	3.23-7.87	<0.001
III	≥20	28 (71.8)	11 (28.2)	10.8	5.14-22.6	<0.001

Values were given as n (%) or OR (95%CI).

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Page 6

Study size	10	Explain how the study size was arrived at	Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6,7,8,11,12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	Page 9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 9
		(*e*) Describe any sensitivity analyses	Page 9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 10
		(b) Give reasons for non-participation at each stage	Page 6,7 and 9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10 and 11
		(b) Indicate number of participants with missing data for each variable of interest	Patients of whom data were missing were excluded.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 11 and 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 11-16

		(*b*) Report category boundaries when continuous variables were categorized	Page 11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 17-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 21-22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of occupational dust exposure with combined chronic obstructive pulmonary disease and pneumoconiosis: a cross-sectional study in China

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Abstract

Objectives Occupational dust exposure may induce various lung diseases, including pneumoconiosis and chronic obstructive pulmonary disease (COPD). The features of combined COPD and pneumoconiosis have not been well described, and this may hamper the management. This study aimed to describe the prevalence and characteristics as well as the risk factors of the combined diseases.

Design A cross-sectional study.

Setting and participants 758 patients with pneumoconiosis were recruited at a single-medical center. Of these, 675 patients with pneumoconiosis, including asbestosis, silicosis, coal workers' pneumoconiosis and other pneumoconiosis, was eligible for analysis.

Primary outcome measures COPD was diagnosed based on clinical features and/or history of exposure to risk factors and post bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio < 0.7. Clinical data were collected from predesigned medical reports. The patients underwent both chest radiograph and high-resolution computed tomography scans. Risk factors for combined COPD and pneumoconiosis were analyzed using regression analysis.

Results COPD prevalence overall was 32.7% (221/675) and was the highest in silicosis (84/221) and coal workers' pneumoconiosis (100/221). COPD prevalence increased with smoking pack-years, dust exposure duration and pneumoconiosis stage. Patients with combined diseases had lower body mass index, higher smoking index and worse pulmonary function. Risk factors for combined diseases included heavy smoking, silica or coal exposure and advanced pneumoconiosis. The interaction between dust exposure and smoking in COPD was also identified. The risk of combined COPD significantly increased with heavy smoking and silica or coal exposure (odds ratio 5.49, 95% confidence interval 3.04–9.93, p<0.001).

Conclusions COPD is highly prevalent in patients with pneumoconiosis, especially patients with silicosis and coal workers' pneumoconiosis. Occupational dust exposure

as well as heavy smoking is associated with an increased risk of combined COPD and pneumoconiosis, which demands an effective preventive intervention.

Keywords: COPD, pneumoconiosis, dust exposure, prevalence, risk factor

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Total word count of the manuscript: 3275 words

Strengths and limitations of this study

- A cross-sectional study was carried out to describe the prevalence and clinical features of combined chronic obstructive pulmonary disease (COPD) and pneumoconiosis.
- The risk factors for the combined diseases were analyzed using regression analysis in a cohort of patients with various subtypes of pneumoconiosis.
- The present study was limited by recruitment of the patients with pneumoconiosis of a single medical centre and the failure to enroll dust-exposed workers without pneumoconiosis.
- The cross-sectional design did not have the power to disclose the association between occupational exposure and disease progression or mortality.

Introduction

Pneumoconiosis is a group of heterogeneous fibrotic lung diseases that develops through the inhalation of the inorganic mineral dusts.[1] Till now, pneumoconiosis is the most common occupational disease in China. In 2018, the prevalence was approximately 90% among the newly reported occupational patients, accounting for about 0.87 million Chinese people with pneumoconiosis.[2] Moreover, pneumoconiosis is a potential cause of disability and thus induces a substantial socioeconomic burden, especially in developing countries.[3 4] A cohort of 110,167 South African miners was found that emphysema remains the occupational lung disease with the highest prevalence.[5] The occupational dust exposures induce lung inflammation cascades and structural damage that can lead dust-related lung disorders including pneumoconiosis as well as chronic obstructive pulmonary disease (COPD).[6]

COPD, characterized by chronic airflow obstruction and persistent respiratory symptoms usually associated with inflammatory response to noxious particles and gasses,[7] is a serious public health problem worldwide.[8-10] In China, the most recent national survey of COPD with 50,991patients enrolled showed the prevalence of spirometry-defined COPD to be 8.6% (11.9% in men and 5.4% in women), representing an estimated 99.9 million population with COPD.[11] Similarly, the 2015 Global Burden of Disease study of 384 million adults found that 174.5million adults were affected by COPD.[12] Cigarette smoking has been identified as the largest risk factor for COPD.[11 13 14] However, numerous other risk factors have been identified,

including several rare genetic syndromes (such as α1-antitrypsin deficiency), underweight, occupational exposures and environmental pollution.[11 15] Specifically, the median population attributable fraction for occupational exposure contribution to COPD risk was 15% and was up to 31% among never-smokers.[13 16 17] Previous research on COPD has mainly focused on the general population or workers with history of exposure to vapor gas, dust and fumes,[18] and few studies have investigated patients with combined COPD and pneumoconiosis, which may be a distinct clinical phenotype. Furthermore, a substantial proportion of pneumoconiosis patients have a history of smoking, and it is unclear whether occupational dust exposure contribution to COPD is equipotent to that of cigarette smoking in some circumstances.

Therefore, the purpose of this study was 1) to describe the prevalence and clinical features of combined COPD and pneumoconiosis and 2) to identify the risk factors for combined disease among pneumoconiosis patients.

Methods

Study design

This descriptive study adopted a cross-sectional design and followed guidelines established by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[19]

Settings and participants

Patients with pneumoconiosis were consecutively recruited, from January 2016 to July 2019, upon presentation at Beijing Chao-Yang Hospital, China, a regional medical center specializing in occupational medicine. The pneumoconiosis was diagnosed according to the International Labour Organization classification after multidisciplinary discussion.[20] Patients of whom spirometry data were missing or with pulmonary malignant tumor, acute pulmonary infection, pulmonary tuberculosis, asthma, bronchiectasis, or pneumothorax were excluded.

All investigations were conducted in accordance with the ethical standards of Beijing Chao-Yang Hospital and the World Medical Association Declaration of Helsinki. The study was approved by the Institutional Review Board (IRB) of Beijing Chao-Yang Hospital. Written informed consent was obtained from all patients.

Sample size

The most influential parameters of sample size were the risk factors for combined COPD and pneumoconiosis. To identify the risk factors for combined diseases, with 95% confidence and 80% power, 5-10 observations per previously demonstrated risk factors for COPD in pneumoconiosis patients were needed.[21] Based on the previous publication by Peng et al,[21] the prevalence of COPD among pneumoconiosis was 18.65%, the calculated sample size was 214 to 428. Furthermore, this study was demonstrated risk factors for COPD in never-smokers subgroup. Thus, the final sample sizes were 498 to 995 according to the proportion of non-smokers in patients with pneumoconiosis from Beijing Chao-Yang Hospital.

Study procedure

Data collection Clinical data were collected from medical reports and included age, sex, height, weight, smoking status, occupational history (including type of exposure, and start and end dates of employment), current and past medical history and family history at the date of inclusion. Smoking status was categorized as: current smoker, former smoker (cessation ≥12 months previously) and never-smoker. Smoking intensity was measured in pack-years (years of smoking 20 cigarettes/day), categorized as: 0 pack-years, 1–9 pack-years, 10–19 pack-years, and ≥20 pack-years, with "heavy smoking" defined as having smoked ≥20 pack-years. Body mass index (BMI) was categorized as: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and overweight/obese (≥25.0 kg/m^2).[11] Latency, defined as the time from initial occupational dust exposure to pneumoconiosis diagnosis, was also recorded.

Pulmonary function tests Pulmonary function tests were carried out by certified technicians according to hospital guidelines, which met the quality control standards established jointly by the American Thoracic Society and European Respiratory Society.[22] Pulmonary function parameters were measured using spirometry, whole body plethysmography, and single-breath diffusing capacity for carbon monoxide measurements. In this study, the pulmonary function prediction formula is based on the normal lung function prediction formula of Chinese adults established in 2017.[23] COPD was diagnosed based on clinical features and/or history of exposure to risk factors and post bronchodilator forced expiratory volume in 1 second (FEV_1)/ forced

vital capacity (FVC) ratio <0.70, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.[24] Similarly, airflow limitation severity was categorized by the percentage of predicted FEV_1, as: mild (≥80%), moderate (≥50% to <80%), severe (≥30% to <50%) and very severe (<30%).[25] Positive bronchial dilation test was defined as an increase in FEV_1 of ≥200 mL and ≥12% after bronchodilation (salbutamol 400mg).[24] Airway hyperresponsiveness (AHR) was defined by a methacholine provocation concentration of 4 mg/mL or less, which led to a 20% reduction in FEV_1 (PC_{20}).[26] Bronchial challenge test was performed in patients with FEV_1 above 60%.

Chest radiographs Chest radiographs were performed for each patient. These were independently assessed by two experienced clinicians according to the International Labor Organization classification,[20] with good interobserver correlation (0.81). Pneumoconiosis was classified as stage Ⅰ, II, or Ⅲ based on the density and distribution of small nodules / large opacities disclosed on the chest X-ray. Further details about the classification criteria can be found in the Supplementary Material (see Method).

High-resolution computed tomography (HRCT) HRCT was acquired on a 64-slice single-source CT system with 0.625–mm sections, a 1–sec scan time and a 10–mm interval in the apex–base scans, with the inclusion of both lungs in the field of view. Large opacity was defined as an opacity having the largest diameter (at the mediastinal window setting) >1 cm. The central type of large opacities, which

compress the bronchus causing airway obstruction, is located between the transverse section of the tracheal carina and a margin 50 mm below the carina. A detailed description of the size of the large opacities is found in the Supplementary Material (see Method).

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 23 (IBM Inc, Chicago, IL, USA). The distribution of the continuous variables was checked at first. Comparisons of normally distributed continuous variables were performed by a one-way analysis of variance (ANOVA) across four groups. The comparisons of non-normally distributed variables were determined using the Mann–Whitney U test or Kruskal-Wallis test. Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were presented as number and percentage and were analyzed using the chi-square test or Fisher's exact test. Univariate and multivariable logistic regression analyses were used to investigate previously demonstrated risk factors for COPD in all pneumoconiosis patients and in never-smokers, respectively, and were reported with odds ratio (OR) and confidence interval (CI). The possible interaction between occupational dust exposure and cigarette smoking was evaluated by Logistic regression analyses. To eliminate the effect of mechanical compression on the bronchi, the patients with large opacities were excluded during Logistic regression analyses. A p-value <0.05 was considered statistically significant.

Patient and public involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Results

Demographics

A total 758 patients were invited to participate between January 2016 and July 2019. Of these, 675 patients with pneumoconiosis (523 men) were included in the analysis. The detailed flow diagram is shown in Figure 1. The sample included 130 patients with asbestosis, 210 with silicosis, 259 with coal workers' pneumoconiosis, and 76 with other subtypes of pneumoconiosis. The demographic characteristics of the groups are presented in Table 1.

Table 1 Demographics of the enrolled population

	All	Asbestosis	Silicosis	Coal workers' pneumoconiosis	Other pneumoconiosis	*p*-value
n	675	130	210	259	76	
Age, yrs	55.0 (49.0-65.0)	67.0 (63.0-72.0)	54.0 (48.0-63.0)	53.0 (49.0-58.0)	47.5 (42.0-55.0)	<0.001
Male	523 (77.5)	65 (50.0)	131 (62.4)	256 (98.8)	71 (93.4)	<0.001
BMI, kg/m^2	25.2±3.4	26.8±3.2	24.9±3.3	24.6±3.5	25.3±3.3	<0.001
Smoking exposure,						
0	290 (43.0)	80 (61.5)	119 (56.7)	71 (27.4)	20 (26.3)	<0.001
1-9	136 (20.1)	14 (10.8)	16 (7.6)	80 (30.9)	26 (34.2)	
10-19	94 (13.9)	10 (7.7)	23 (11.0)	48 (18.5)	13 (17.1)	
≥20	155 (23.0)	26 (20.0)	52 (24.8)	60 (23.2)	17 (22.4)	

Cumulative pack-yrs	15.0 (5.0-25.0)	21.3 (7.4-40.0)	20.0 (11.3-30.0)	10.5 (3.8-22.5)	10.0 (3.0-23.8)	<0.001
Duration of exposure, yrs	12.0 (7.0-20.0)	8.5 (5.0-14.3)	13.0 (8.0-21.3)	14.0 (6.0-20.0)	11.0 (8.0-17.5)	<0.001
Latent period, yrs	26.0 (13.0-35.0)	47.5 (36.5-52.0)	26.0 (18.0-34.0)	22.0 (9.0-29.0)	12.0 (8.0-22.8)	<0.001
Stage of pneumo.						<0.001
Ⅰ	332 (49.2)	85 (65.4)	95 (45.2)	89 (34.4)	63 (82.9)	
Ⅱ	164 (24.3)	39 (30.0)	44 (21.0)	72 (27.8)	9 (11.8)	
Ⅲ	179 (26.5)	6 (4.6)	71 (33.8)	98 (37.8)	4 (5.3)	

Data was presented as mean ± SD or n (%) or median (IQR).

Abbreviations: BMI: body-mass index; IQR: interquartile range.

Prevalence of combined COPD and pneumoconiosis

The overall prevalence of COPD was 32.7% (221/675) in the enrolled population (Table 2). The prevalence of COPD was significantly different among the subgroups, and patients with silicosis and coal workers' pneumoconiosis had relatively high prevalence (40.0% and 38.6% respectively). The prevalence of COPD increased with smoking pack-years and was 24.3%, 36.2% and 43.9%, respectively, in the patients smoking1–9 pack-years, 10–19 pack-years, and ≥20 pack-years (p<0.002). Similarly, the prevalence increased with the duration of dust exposure and was 30.0% with 0–15 years, 36.9% with 16–30 years and 39.6% with 31–45 years of exposure (p<0.046). The prevalence of COPD also increased with the pneumoconiosis stage and was 20.2% in stage Ⅰ, 25.6% in stage Ⅱ and 62.6% in stage Ⅲ (p<0.001). The prevalence of COPD did not differ by sex, smoking history or BMI.

Table 2 Prevalence of combined COPD and pneumoconiosis

	All		COPD and pneumoconiosis		
	n	%	n	%	p-value

Overall	675	100	221	32.7	
Pneumoconiosis					<0.001
Asbestosis	130	19.3	23	17.7	
Silicosis	210	31.1	84	40.0	
Coal workers' pneumoconiosis	259	38.4	100	38.6	
Other pneumoconiosis	76	11.3	14	18.4	
Age, yrs					0.083
20-29	3	0.4	0	0	
30-39	25	3.7	4	16.0	
40-49	164	24.3	37	22.6	
50-59	222	32.9	95	42.8	
60-69	178	26.4	60	33.7	
≥70	83	12.3	25	30.1	
Male	523	77.5	177	33.8	0.258
Smoking history					0.089
Never-smoker	290	43.0	86	29.7	
Former smoker	183	27.1	68	37.2	
Current smoker	202	29.9	67	33.2	
Smoking exposure, pack-yrs					0.002
0	290	43.0	86	29.7	
1-9	136	20.1	33	24.3	
10-19	94	13.9	34	36.2	
≥20	155	23.0	68	43.9	
BMI, kg/m^2					0.228
<18.5	7	1.0	3	42.9	
18.5-24.9	330	48.9	115	34.8	
≥25.0	338	50.1	103	30.5	
Duration of exposure, yrs					0.046
0-15	424	62.8	127	30.0	
16-30	198	29.3	73	36.9	
31-45	53	7.9	21	39.6	
Stage of pneumoconiosis					<0.001
Ⅰ	332	49.2	67	20.2	
Ⅱ	164	24.3	42	25.6	
Ⅲ	179	26.5	112	62.6	

Abbreviations: COPD: chronic obstructive pulmonary disease; BMI: body-mass index.

Characteristics of the patient with combined COPD and pneumoconiosis

In comparison with pneumoconiosis alone, the patients with combined COPD and pneumoconiosis had higher cigarette pack-years (p<0.001), lower BMI (p=0.001), higher silica or coal dust exposure (p<0.001) as well as higher stage (p<0.001) (Table 3). The patients with combined COPD and pneumoconiosis also differed from those with only pneumoconiosis in a range of lung function measures (Table S1); in particular, compared with those without COPD, patients with COPD had significantly more severe airflow limitation, increased small airway dysfunction and decreased membrane diffusing capacity.

Among the 221 patients with COPD and pneumoconiosis, 31.7% had GOLD stage I COPD; 42.1% had stage II; 20.8% had stage III, and 5.4% had stage IV (Table S2). Additionally, 29.4% (65/221) patients with combined diseases had a positive bronchodilation test, 57.1% (64/112) had AHR, and 43.9% (97/221) had blood eosinophil counts >100 cells/μL (Table S2).

Risk factors for combined COPD and pneumoconiosis

In the full study sample, 9.5% (20/210) of the patients with silicosis and 1.5% (4/259) of the patients with coal workers' pneumoconiosis showed central of large opacities on HRCT, who were excluded during the logistic regression analyses. In the univariate logistic regression analysis, the risk factors associated with COPD included

Table 3 A composition of pneumoconiosis combined with or without COPD

	COPD and pneumoconiosis	Pneumoconiosis alone	*p*-value
n	221	454	
Age, yrs	56.0 (51.0-63.5)	55.0 (48.0-65.3)	0.086
Male	177 (80.1)	346 (76.2)	0.258
Smoking exposure, pack-yrs			
0	86 (38.9)	204 (44.9)	0.002
1-9	33 (14.9)	103 (22.7)	
10-19	34 (15.4)	60 (13.2)	
≥20	68 (30.8)	87 (19.2)	
Cumulative pack-yrs	20.0 (10.0-30.0)	10.9 (4.0-22.5)	<0.001
BMI, kg/m^2	24.7 (22.2-26.7)	25.1 (23.3-27.9)	0.001
Duration of exposure, yrs	13.0 (7.0-20.0)	11.0 (6.0-19.0)	0.068
Latency period, yrs	25.0 (14.0-33.0)	26.0 (12.0-39.0)	0.320
Stage of pneumoconiosis			<0.001
Ⅰ	67 (30.3)	265 (58.3)	
Ⅱ	42 (19.0)	122 (26.9)	
Ⅲ	112 (50.7)	67 (14.8)	
Exposure dust			<0.001
Asbestos	23 (10.4)	107 (23.6)	
Silica	84 (38.0)	126 (27.8)	
Coal	100 (45.2)	159 (35.0)	
Other dust	14 (6.3)	62 (13.7)	
Symptoms			
Cough	171 (77.4)	329 (72.5)	0.172
Sputum production	123 (55.7)	219 (48.2)	0.070
Dyspnea	129 (58.4)	264 (58.1)	0.956

Data was presented as n (%) or median (IQR).

Abbreviations: COPD: chronic obstructive pulmonary disease; BMI: body-mass index.

age ≥40 years, heavy smoking, silica or coal exposure and pneumoconiosis stage Ⅲ (Table 4). In the multivariable-adjusted analyses, the risk of COPD was increased among patients with exposure to silica (OR 2.42, 95%CI 1.28-4.59, p=0.007) and coal (OR 3.19, 95%CI 1.57-6.49, p=0.001) dust, compared with patients with exposure to

asbestos; there was a significantly increased risk of COPD in pneumoconiosis stage Ⅲ compared with stages Ⅰ/Ⅱ (OR 4.85, 95% CI 3.18-7.42, p<0.001).

Among the never-smokers, multivariable-adjusted analyses showed that the risk of COPD was increased with silica exposure (OR 3.88, 95%CI 1.49-10.12, p=0.006), and coal (OR 3.85, 95%CI 1.12-13.18, p=0.032) compared with asbestos exposure, consistent with the results for the full sample (Table S3).

Interaction between occupational dust exposure and cigarette smoking

A significant interaction was found between occupational exposure and cigarette smoking (Table S4 and Figure 2). The risk of COPD increased with heavy smoking and silica or coal exposure (OR 5.49, 95%CI 3.04–9.93, p<0.001). Similarly, a significant interaction was noted between smoking intensity and pneumoconiosis stage.

Table 4 Logistic regression model for 651 patients with combined COPD and pneumoconiosis*

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Age, yrs						
20-39	1.00	(ref)		1.00	(ref)	
40-59	3.86	1.14-13.06	0.030	2.33	0.64-8.54	0.202
≥60	3.46	1.01-11.82	0.048	3.76	0.97-14.7	0.056
Male gender	1.22	0.81-1.83	0.340	0.81	0.43-1.50	0.498
Smoking exposure, pack-yrs						
0	1.00	(ref)		1.00	(ref)	
1-19	1.01	0.68-1.49	0.980	0.92	0.55-1.56	0.761
≥20	2.01	1.32-3.06	0.001	1.91	1.10-3.32	0.022

BMI[#], kg/m^2						
<18.5	1.05	0.19-5.85	0.952	0.54	0.79-3.67	0.527
18.5-24.9	1.00	(ref)		1.00	(ref)	
≥25.0	0.87	0.63-1.22	0.431	1.09	0.75-1.58	0.664
Exposure duration, yrs						
0-15	1.00	(ref)		1.00	(ref)	
16-30	1.25	0.86-1.82	0.233	0.78	0.51-1.19	0.246
31-45	1.48	0.81-2.71	0.207	1.28	0.62-2.64	0.503
Exposure type						
Asbestos	1.00	(ref)		1.00	(ref)	
Silica	2.48	1.44-4.25	0.001	2.42	1.28-4.59	0.007
Coal	2.86	1.70-4.79	<0.001	3.19	1.57-6.49	0.001
Other dust	1.05	0.50-2.19	0.895	1.89	0.80-4.46	0.147
Stage of pneumoconiosis						
Ⅰ / Ⅱ	1.00	(ref)		1.00	(ref)	
Ⅲ	5.05	3.44-7.41	<0.001	4.85	3.18-7.42	<0.001
BDT						
Negative	1.00	(ref)		1.00	(ref)	
Positive	2.07	0.76-5.61	0.153	2.17	0.67-7.01	0.197

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate; BMI: body-mass index; BDT: bronchial dilation test.

*All variables in the table were included in the multivariate model, while adjusting for age, sex, BMI, exposure duration, and BDT.

[#] The patients with BMI <18.5 kg/m^2 means under weight, 18.5-24.9 kg/m^2 means normal range, and ≥25.0 kg/m^2 means overweight and obese.

Discussion

The present study disclosed that COPD was highly prevalent in the patients with certain types of pneumoconiosis. The results also showed the characteristics and risks for combined COPD and pneumoconiosis. The prevalence of COPD differed according to the type of pneumoconiosis and was the highest in silicosis, followed by coal workers' pneumoconiosis. Patients with both COPD and pneumoconiosis had higher cigarette pack-years, lower BMI, higher composition of silica or coal dust exposure as well as higher percent of stage Ⅲ, more severe airflow limitation and

increased small airway dysfunction, compared with patients with pneumoconiosis alone. Heavy smoking, silica or coal dust exposure and advanced pneumoconiosis were identified as the preventable risk factors for COPD in patients with pneumoconiosis. A positive interaction was found between occupational dust exposure and cigarette smoking among patients with combined COPD and pneumoconiosis.

Previous population-based studies have reported different prevalence of COPD in various countries and on populations with a variety of occupations.[11 27 28] Data from 418,378 adult respondents to the 2017 Behavioral Risk Factor Surveillance System survey showed that the overall age-adjusted prevalence of COPD was 6.2% in the United States.[29] Similarly, the most recent population-based study from China reported an overall COPD prevalence of 8.6%.[11] Our data showed a particularly high prevalence of COPD among patients with pneumoconiosis, especially in silicosis and coal workers' pneumoconiosis. Across-sectional study of patients with silicosis or coal workers' pneumoconiosis from South China reported a COPD prevalence of 18.65% (119/638), which is lower than our finding.[21] One reason may be that our study had a higher percentage of smokers. It is also possible that the differences in COPD prevalence are a result of other differences in study participants and working conditions. The present study also found that over half (57.0%) of the patients were smokers and that the prevalence of COPD did not differ between smokers and nonsmokers—these findings are in line with the data previously reported.[21] While these earlier studies are not directly comparable, the data indicate that combined

COPD and pneumoconiosis occurs often in patients with certain types of pneumoconiosis.

Silica, coal, asbestos and mixed dusts are common occupational respiratory toxins. One study found the prevalence of emphysema to be higher in the patients with silica exposure (55%) than in those with asbestos exposure (29%) (p=0.04).[30] Another study from South Africa also showed that the rate (per 1000 autopsies) of emphysema was higher with coal exposure (404/1000) than with asbestos exposure (345/1000).[31] Similarly, in the present study, the prevalence of COPD was twice as high in patients with silicosis and patients with coal workers' pneumoconiosis than in those with asbestosis. Of note, our previous study found that even in the presence of both emphysema and pulmonary fibrosis, spirometry and lung volumes may still be in normal range or show mild abnormalities, such as the small airway dysfunction.[32] Thus, it is possible that COPD was underestimated in patients with pneumoconiosis, especially asbestosis.[32] Additionally, we found that pneumoconiosis severity was associated with COPD prevalence. This finding is consistent with previous data showing that the prevalence of emphysema increases with pneumoconiosis stage—as high as 60.76% (144/237) in pneumoconiosis stage Ⅲ.[33] These results suggest that airflow obstruction is associated with the severity of pneumoconiosis.[34 35]

The high prevalence of COPD in our sample of patients with pneumoconiosis underscores the importance of identifying the risk factors for combined COPD and pneumoconiosis. Cigarette smoking has been well recognized as one of the main risk

factors for development of COPD.[11 36 37] In the present study, smoking pack-years was associated with increased risk of COPD. However, in previous research, no significant correlation was found between smoking and COPD in patients with pneumoconiosis.[21] A possible explanation of the inconsistency is the lack of stratification by smoking pack-years in the earlier work. Previous studies of COPD have examined occupational risk factors in addition to smoking. An earlier meta-analysis showed that occupational exposure to irritant dusts, gases and fumes was an independent risk factor for COPD.[38] Several studies have found that compared with asbestos dust, silica and coal dust exposure is more strongly associated with emphysema.[30 39 40] Similarly, the present study provides confirmation that exposure to silica or coal dust results in a higher risk for COPD than asbestos exposure does, both in smokers and never-smokers. These findings support the hypothesis that patients with silica and coal dust exposure suffer from higher dust concentrations or more damaging components (compared with asbestos), resulting in elevated risk for COPD. Inhaled silica and coal dust are predominantly deposited in the bronchioles, where they are engulfed by alveolar macrophages,[41-43] whereas inhaled asbestos fibers accumulate in the peribronchiolar and adjacent alveolar spaces.[44] Thus, different types of dust inflict varying damage to the lungs, but chronic inflammation, remodeling of the small airways and destruction of lung parenchyma ultimately lead to COPD.[45 46] Moreover, the higher OR for COPD among never-smokers compared with the full sample suggests that silica and coal dust exposures contribute more substantially to the burden of COPD in nonsmokers. Additionally, a longitudinal cohort study of

3,202 patients with silicosis in Hong Kong demonstrated interactive effects of cigarette smoking and silicosis on COPD.[47] Our study also indicates that smoking potentiates the effect of silica and coal dust exposure on COPD, consistent with the findings from other previous studies.[48-50] Thus, smoking cessation, in addition to prevention of occupational exposure, is critical to reducing COPD-related morbidity.

Among the full sample of patients with pneumoconiosis in the present study, nearly three-quarters of the cases of COPD were mild to moderate in severity (by GOLD staging). The decline in lung function appears to result primarily from obstructive rather than restrictive air trapping. One-half of patients with combined COPD and pneumoconiosis had AHR, but this was not significantly different from the finding of AHR in patients with pneumoconiosis alone. An earlier study reported that 24%–60% of patients with COPD had AHR.[51-53] However, little is known about the clinical features of combined COPD and pneumoconiosis. A post hoc analysis of three randomized trials that included 4,528 patients with COPD treated by inhaled corticosteroids (ICS) found a reduction in exacerbation at blood eosinophil levels >100 cells/μL (relative risk =0.75).[54] Elsewhere, it was suggested that a threshold of ≥300 cells/μL can identify patients with the greatest likelihood of beneficial response to ICS.[54 55] Based on these studies, the 43.9% (97/221) of the patients with combined disease with blood eosinophil counts ≥100 cells/μL (or the 7.5% with counts >300 cells/μL) in the present study are likely to benefit from ICS. Nevertheless, it is uncertain whether blood eosinophil count is a reliable biomarker for response to ICS treatment for the prevention of exacerbations of combined COPD and

pneumoconiosis. Clinical trials are warranted to evaluate the effectiveness of ICS therapy in this regard.

This study had several limitations. First, this study recruited patients from a single medical centre and did not investigate dust-exposed workers without pneumoconiosis. Second, the cross-sectional design did not disclose the association between occupational exposure and disease progression or mortality—longitudinal, population-based studies are warranted to identify the role of occupational dust exposure in the development and prevention of COPD. Third, since the patients in the study were employed by different industries, it was difficult to estimate occupational exposure levels and therefore the exposure-response relationship in COPD prevalence. Finally, the effect of passive smoke was not taken into account in our study. The effects of smoking on COPD might be underestimated.

Conclusion

The present study showed that COPD was highly prevalent in the patients with certain types of pneumoconiosis. More than 70% of patients with combined COPD and pneumoconiosis had mild-to-moderate airflow limitation. Nearly half of them had peripheral eosinophil count >100/μL. Heavy smoking, silica or coal dust exposure and advanced pneumoconiosis are all associated with increased COPD risk, although differences in the onset of COPD before or after the onset of pneumoconiosis cannot be distinguished. In addition, occupational dust exposure interacts with smoking to further increase the risk of COPD. Our study indicates that the prevention measures

are critical to decrease the occupational exposure and improve the disease controlling among dust exposure workers. Meanwhile, tobacco education and smoking cessation are needed to recognize and control smoking hazards.

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Footnotes

Contributors: Y Fan performed all data collection, analyzed and wrote the manuscript. W Xu and Y Wang were responsible for acquisition of data and data analysis. Y Wang and S Yu were responsible for recruiting the patients and acquisition of data. Q Ye contributed as primary investigator and was involved in the conception, design and planning the study, the acquisition of data, revision of the paper. All authors contributed to data interpretation, read and approved the final manuscript.

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Figure legends

Figure 1. Flow chart of the enrolled population

Figure 2. Interactions between risk factors for combined COPD and pneumoconiosis: (A) occupational dust exposure and cigarette smoking, (B) pneumoconiosis stage and cigarette smoking

Abbreviation: COPD: chronic obstructive pulmonary disease.

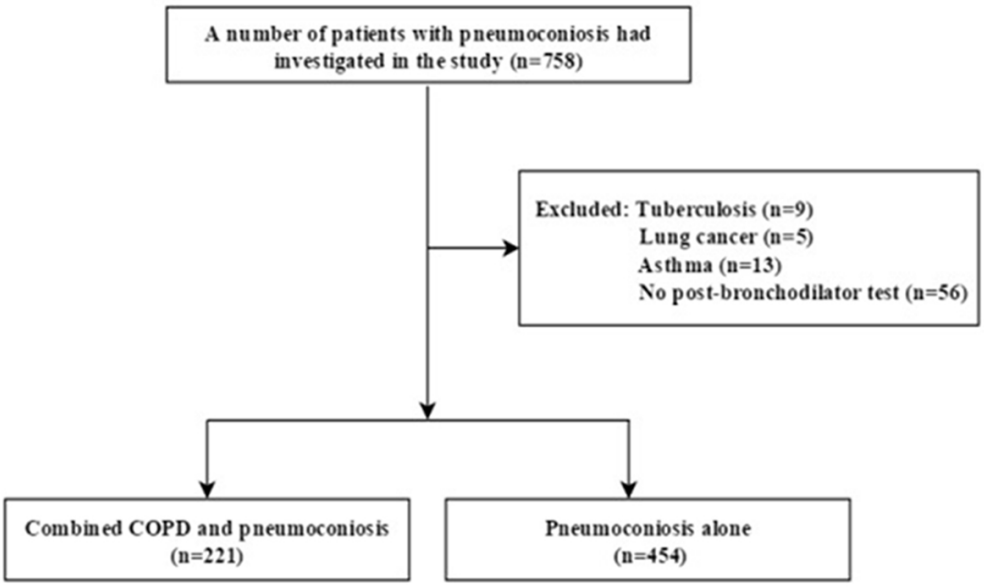

Figure 1. Flow chart of the enrolled population

99x60mm (300 x 300 DPI)

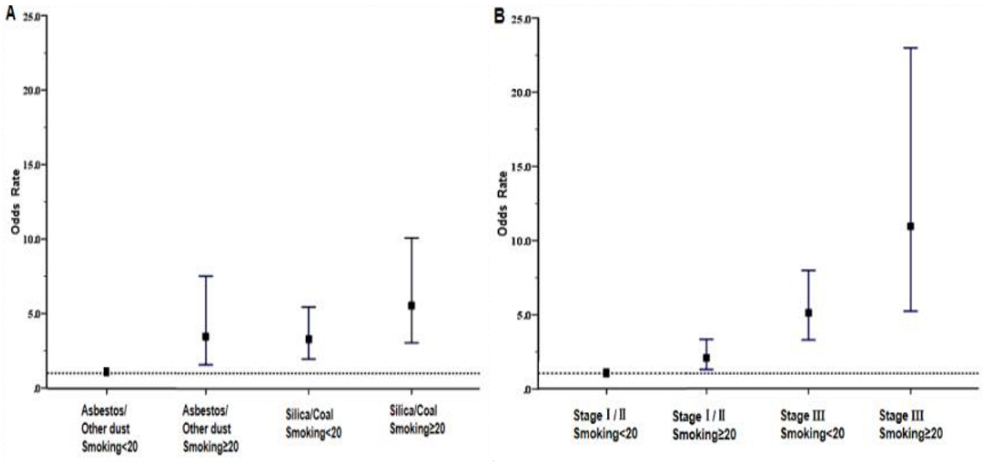

Figure 2. Interactions between risk factors for combined COPD and pneumoconiosis: (A) occupational dust exposure and cigarette smoking, (B) pneumoconiosis stage and cigarette smoking
Abbreviation: COPD: chronic obstructive pulmonary disease.

Supplimentary files

Methods

Classification of pneumoconiosis by chest radiograph

Pneumoconiosis was classified into three stages according to the International Labour Organization classification system.[1] Briefly, each lung field was divided into three zones (upper, middle, lower) on the posterior chest radiographs. When the highest density of small opacities was ≥1/0, the distribution affected two or more zones and pleural plaques were apparent, the patients were diagnosed as Stage I. When the highest density of small opacities was ≥2/1 and the distribution affected more than four zones, or the highest density of small opacities was ≥3/2 and the distribution affected four or more zones, the patients were diagnosed as Stage II. When the highest density of small opacities was ≥3/2 and the distribution affected four or more zones with aggregation of small or large opacities, or the diameter of the largest opacity was ≥20 × 10 mm, the patients were diagnosed as Stage III. The interobserver correlation was good, and the κ value was 0.81.

High-resolution computed tomography

The size of large opacities were categorized as follows: (1) Type A: one or more opacities with total area ≤1/4 of the right side of the CT slice at the carina; (2) Type B: one or more opacities with total area >1/4 and ≤1/2 of the area of the right side of the CT slice at the carina; and (3) Type C: one or more opacities with total area >1/2 of

the right side of the CT slice at the carina.[2] Two experts independently assessed the presence of large opacity on HRCT, according to the International Classification of HRCT for Occupational and Environmental Respiratory Diseases (ICOERD),[2] with good interobserver correlation (0.78).

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Table S1 Pulmonary function tests of the patients with combined COPD and pneumoconiosis

Variables	All (n=675)	COPD and pneumoconiosis (n=221)	Pneumoconiosis alone (n=454)	*p*-value
FVC, %pred	97.80 (82.30-109.40)	91.25 (76.00-109.18)	99.40 (85.50-110.15)	0.001
FEV_1, %pred	88.80 (71.40-102.20)	68.25 (49.45-86.33)	95.00 (82.80-105.95)	<0.001
FEV_1/FVC, %	74.18 (66.18-79.92)	61.21 (50.76-66.35)	77.97 (74.00-81.81)	<0.001
DLco SB, %pred	86.10 (68.20-99.60)	79.40 (60.25-92.95)	89.30 (74.25-100.65)	<0.001
TLC, %pred	93.50 (81.40-102.90)	99.30 (87.30-109.73)	90.50 (79.45-99.65)	<0.001
RV, %pred	102.20 (86.30-121.15)	120.95 (101.43-146.30)	95.00 (82.20-111.90)	<0.001
RV/TLC, %	40.53 (34.83-48.10)	46.47 (39.71-54.45)	37.81 (33.07-44.55)	<0.001
PEF, %pred	93.25 (74.23-109.00)	68.90 (46.43-86.05)	101.60 (89.00-115.10)	<0.001
MEF_{75}, %pred	79.10 (52.75-105.00)	41.20 (22.95-56.55)	95.30 (77.25-112.60)	<0.001
MEF_{50}, %pred	58.40 (38.40-79.50)	29.45 (18.10-41.48)	72.50 (56.05-89.45)	<0.001
MEF_{25}, %pred	45.65 (29.70-61.90)	28.05 (19.75-37.35)	56.00 (42.40-69.95)	<0.001
PaO_2, mmHg	89.00 (83.00-96.00)	87.00 (81.00-93.00)	91.00 (85.00-97.00)	<0.001
CPI	13.80 (4.22-26.11)	15.78 (3.47-27.10)	12.90 (4.57-24.55)	0.314

Values were given as the median (IQR).

Abbreviations: FVC: forced vital capacity; FEV_1: forced expired volume in the first second; DLco SB: diffusion capacity for carbon monoxide of the lung single breath; TLC: total lung capacity; RV: residual volume; PEF: peak expiratory flow; MEF_{25}: maximal expiratory flow after 25% of the FVC has been not exhaled. MEF_{50}: maximal expiratory flow after 50% of the FVC has been not exhaled; MEF_{75}: maximal expiratory flow after 75% of the FVC has been not exhaled; PaO_2: arterial partial pressure of oxygen; CPI: composite physiologic index; IQR: interquartile range.

Table S2 Characteristics of 221 patients with combined COPD and pneumoconiosis

COPD and pneumoconiosis	n	%
Classification of airflow limitation severity*		
GOLD stage I	70	31.7
GOLD stage II	93	42.1
GOLD stage III	46	20.8
GOLD stage IV	12	5.4
BDT, positive	65	29.4
AHR†	64	57.1
Blood eosinophil count		
≥100 cells/μL	97	43.9
≥300 cells/μL	17	7.5

Abbreviations: COPD: chronic obstructive pulmonary disease; BDT: bronchial dilation test; AHR: airway hyperresponsiveness.

* GOLD stage I: mild, FEV_1 ≥80% predicted; GOLD stage II: moderate, FEV_1 ≥50% to <80% predicted; GOLD stage III: severe, FEV_1 ≥30% to <50% predicted; GOLD stage IV: very severe, FEV_1<30% predicted.

†Bronchial challenge test was performed in patients with FEV_1 predicted more than 60%. In present cohort of combined COPD and pneumoconiosis, 57.1% (64/112) was shown AHR.

Table S3 Logistic regression model for 280 combined COPD and pneumoconiosis in nonsmokers

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age, yrs						
20-39	1.00	(ref)		1.00	(ref)	
40-59	NS			NS		
≥60	NS			NS		
Male gender	0.92	0.54-1.57	0.770	0.95	0.43-2.08	0.946
BMI, kg/m^2						
<18.5 (underweight)	NS			NS		
18.5-24.9 (Normal)	1.00	(ref)		1.00	(ref)	
≥25.0 (Overweight and	1.06	0.62-1.80	0.846	1.35	0.735-2.47	0.335
Exposure duration, yrs						
0-15	1.00	(ref)		1.00	(ref)	
16-30	1.22	0.65-2.27	0.533	0.85	0.41-1.75	0.651
31-45	0.69	0.19-2.54	0.576	0.67	0.16-2.87	0.590
Exposure type						
Asbestos	1.00	(ref)		1.00	(ref)	
Silica	2.76	1.35-5.63	**0.005**	3.88	1.49-10.12	**0.006**
Coal	2.47	1.14-5.36	**0.022**	3.85	1.12-13.18	**0.032**
Other dust	0.57	0.12-2.77	0.488	1.18	0.21-6.72	0.849
Stage of pneumoconiosis						
I/II	1.00	(ref)		1.00	(ref)	
III	4.93	2.65-9.17	**<0.001**	4.74	2.38-9.43	**<0.001**
BDT						
Negative	1.00	(ref)		1.00	(ref)	
Positive	1.57	0.85-2.87	0.147	1.50	0.75-3.03	0.256

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate; BMI: body-mass index; BDT: bronchial dilation test.

Table S4 Cumulative effects of cigarette smoking with occupational exposure on COPD in pneumoconiosis

		COPD and pneumoconiosis	Pneumoconiosis alone	OR	95%CI	*p*-value
Exposure type	Smoking status					
Asbestos/Other dust	<20	22 (13.5)	141 (86.5)	1.00	(ref)	
Asbestos/Other dust	≥20	15 (34.9)	28 (65.1)	3.43	1.59-7.43	0.002
Silica/Coal	<20	115 (33.7)	226 (66.3)	3.26	1.97-5.39	<0.001
Silica/Coal	≥20	48 (46.2)	56 (53.8)	5.49	3.04-9.93	<0.001
Stage of pneumoconiosis	Smoking status					
I/II	<20	74 (19.1)	314 (80.9)	1.00	(ref)	
I/II	≥20	35 (32.4)	73 (67.6)	2.03	1.26-3.27	0.003
III	<20	63 (54.3)	53 (45.7)	5.04	3.23-7.87	<0.001
III	≥20	28 (71.8)	11 (28.2)	10.8	5.14-22.6	<0.001

Values were given as n (%) or OR (95%CI).

Abbreviations: COPD: chronic obstructive pulmonary disease; OR: odds rate.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Page 6

Study size	10	Explain how the study size was arrived at	Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6,7,8,11,12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	Page 9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 9
		(*e*) Describe any sensitivity analyses	Page 9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 10
		(b) Give reasons for non-participation at each stage	Page 6,7 and 9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10 and 11
		(b) Indicate number of participants with missing data for each variable of interest	Patients of whom data were missing were excluded.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 11 and 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 11-16

		(*b*) Report category boundaries when continuous variables were categorized	Page 11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 17-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 21-22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.